Consequences of Detecting and Pursuing Incidental Findings on Computed Tomographic Colonography Screening in Average-risk Populations

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Structured Abstract

Objective

To weigh the benefits and harms of detecting and pursuing incidental findings on computed tomographic colonography screening in average-risk populations.

Data Sources

I searched MEDLINE, EMBASE, ScienceDirect, and the Cochrane Collaboration library from 1996 to present, with all searches limited to English language studies.

Study Selection

I developed inclusion and exclusion criteria to examine an average-risk population.

Data Extraction

I performed a single data extraction from included studies of fair to good quality for the preparation of evidence tables. I rated the quality of the selected studies using criteria modified from those recommended by the USPSTF for study appraisal.

Data Synthesis

Key Question #1: What is the prevalence of all incidental findings detected on CTC? At least one extracolonic finding was detected in 62% of screened patients. 5.9% of patients received additional investigations. One study examined the effects of IV contrast-enhancement. This study reported a lower frequency of patients receiving additional investigation than any of the other studies.

Key Question #2: What is the prevalence of specific types of incidental findings? Two studies reported the specific types of findings that were ultimately diagnosed. The most common diagnosed pathologies reported in these studies were

nonmalignant tumors (1.5% of screened populations), malignant tumors (0.5% of screened populations) and aortoiliac aneurysms (0.3% of screened populations)

Key Question #3: What are the beneficial outcomes of detecting and investigating incidental findings? Three studies reported a total of 114 patients (at least 2.3% of all patients) who received clinical diagnoses. It is uncertain how many of these received treatment, but at least 0.9% of all patients received treatment. The true benefit of pursuing incidental findings is unlikely to include all of the diagnosed and treated pathologies.

Key Question #4: What are the harms of detecting and investigating incidental findings? One study reported the number of patients who received additional workup with no reported diagnoses. Underestimated extrapolated values were obtained for two studies. Approximately 3.1% of the patients from these three studies received additional workup with no reported important clinical diagnoses; this value may overestimate the true value. Three studies reported data on invasive procedures that resulted in benign findings. At least 0.5% of patients in these three studies received an invasive procedure that resulted in the diagnosis of a benign finding. All of the patients who receive further investigations with no diagnoses or treatment experience at least some degree of harm.

Key Question #5: What are the costs and cost-effectiveness of detection and further investigating incidental findings? The cost of pursuing incidental findings likely falls between $98.56 and $248. Cost-effectiveness analysis cannot be assessed without a more comprehensive evaluation of the benefits and harms.

Conclusion

Incidental findings are found in over half of asymptomatic patients who are screened by CTC. The number of patients who receive additional investigations is much fewer. A small percentage of patients receive clinical diagnoses and treatment. Clinical benefit likely results from some, but not all, of these patients receiving diagnoses and treatment. Likewise, a small percentage of screened subjects received additional workup with no reported diagnoses. All of these received at least some degree of harm. The degree of benefit and harm resulting from each diagnoses, treatment, or additional workup remains unclear. This further complicates the task of weighing the benefits versus the harms. Available data is insufficient to appropriately weigh the overall benefits versus the overall harms.

Introduction and Background

The Problem

Screening is the strategy used to detect disease or risk factors for a disease in individuals without signs or symptoms of the disease.[1] Screening tests are imperfect. Their ability to detect targeted pathology is accompanied by the ability to detect non-targeted, or incidental, findings. As a screening test's sensitivity (ability to detect true positive findings) increases, so does its tendency to detect other non-targeted findings. Because of this attribute, the overall value of a screening test depends not only on its ability to detect the targeted pathology, but also on the consequences of detecting non-targeted lesions.

In recent years, researchers have explored the feasibility of using highly sensitive tests, such as CT and MRI, as widespread screening tools with the ultimate hope of providing improved outcomes. Several large scale CT screening studies have been conducted for colorectal and lung cancers, and the American Cancer Society now recommends MRI as an adjunct screening tool in women at high risk for breast cancer.[2] CT imaging furthermore portrays data on body regions that include much more than the targeted organs. Because of this, CT imaging has the ability to detect untargeted, or incidental, findings.[3] An incidental finding is generally defined as an abnormality not related to the indication for obtaining a test.[4] Concerning CT, "every abnormal finding not directly related to the pathophysiology of the targeted disease should be regarded as incidental."[4] The ability to detect these subtle abnormalities has come with an increased likelihood of incidental findings, calling more attention to the uncertain consequences of

their detection. This systematic review addresses the consequences, both benefits and harms, of CT screening for colorectal cancer.

Evaluation of Screening Tests

An understanding of the basic principles of diagnostic test interpretation gives perspective to the detection of incidental findings. The predictive value of a diagnostic test – the probability of disease given the results of a test – is not a property of the test alone but is also dependent on the prevalence (or pretest probability) of disease in the population being tested. Because the prevalence of most diseases, particularly those found incidentally, is low in asymptomatic populations, the positive predictive value is low, even for tests with high specificity. Positive results, when applied to patients with a low likelihood of having the disease, will largely be false positives.[1]

The interpretation of a positive or negative diagnostic test result varies from setting to setting, according to the pretest probability of disease in a particular setting.[1] Colorectal cancer possesses a sufficient prevalence in the general population of men and women aged 50 to 75[5] in which a screening program can provide more benefit than harm. Incidental findings, on the other hand, are not detected in a specific population in which their true disease states are more prevalent but are instead discovered in a population with a negligible pretest probability[6], increasing the probability of a positive test to be false.

Colorectal Cancer Screening

The ultimate goal of cancer screening is to decrease cancer-related mortality and to improve quality of life by detecting curable cancer in its preclinical state. Therefore,

in addition to an effective screening tool it is also important to have a treatment whose efficacy is greater in the preclinical (asymptomatic) phase than in the clinical (symptomatic) phase for a screening program to be effective.

Randomized controlled trials have found that the efficacy of colorectal cancer screening with fecal occult blood testing (FOBT) has been demonstrated to reduce colorectal cancer mortality by 15% to 33% in randomized, controlled trials.[7,8,9] The relative mortality reduction for colonoscopy screening is unknown, but is presumed to be larger than FOBT. During their 2002 systematic review, the U.S. Preventive Services Task Force (USPFTF) did not find any screening trials of colonoscopy but analyzed data from the National Polyp Study and a case-control study to draw these conclusions.[10] For these evidence-based reasons, screening guideline recommendations for colorectal cancer are widely accepted.

Problems with Colonoscopy

Colonoscopy, the gold standard for colorectal cancer screening, carries a variety of problems. Major medical risks associated with colonoscopy include damage to the colon or rectum, including perforation, adverse reaction to medications (largely sedation medications), serious infection, and cardiovascular complications. The main limit to colonoscopy screening effectiveness is poor adherence.[11] Many factors contribute to the lack of adherence to a screening colonoscopy regimen. These include discomfort with the invasiveness of colonoscopy and the potential for such serious complications as perforation or severe bleeding. In addition to the medical complications and lack of

adherence, colonoscopies are costly, averaging $3323 – $5000 or more[11] per procedure in the hospital setting.

Potential Benefits of Computed Tomographic Colonography

Computed tomographic colonography (CTC) is a promising tool that has the potential to help increase overall participation in screening of the population.[12] In contrast to conventional colonoscopy, the CTC procedure is less time-consuming and is less invasive. No sedation is required and the patient can return to his/her usual activities after the procedure without the aid of another person. Although CTC does require the same pre-procedural preparation as colonoscopy (colonic cleansing and insufflations), the degree of perceived discomfort is much less than that of the invasive colonoscopy. The implementation of a CTC screening program aims to decrease the number of standard colonoscopies performed per patient screened. Only those patients with polyps identified on CTC will be sent for standard colonoscopy and polyp resection. By offering the advantage of a "very low" risk of bowel perforation[5] compared to conventional colonoscopy, many researchers are optimistic that such a program will reduce the number of complications per patient screened.

CTC has been shown to be effective in detecting colonic lesions in the asymptomatic population.[13] In a 2008 systematic review for the United States Preventive Service Task Force (USPSTF), Whitlock et al examined 7 studies examining a total of 4468 average-risk patients screened for colorectal cancer with both CTC and conventional colonoscopy. Three of the studies did not contribute to quantitative test performance analysis due to study design limitations.[5] The two largest and most

applicable studies, which accounted for 87% of the observed patients, were those by Pickhardt et al and by the American College of Radiology Imaging Network (ACRIN). These studies found that the performance of CTC was comparable to conventional colonoscopy for detection of large polyps (≥10mm) with a pooled sensitivity of 92% (CI, 87% to 96%) and no statistical heterogeneity.[5, 14, 15]

Uncertainties of CTC

Though CTC carries a much decreased risk of many medical complications associated with colonoscopy, it holds a different set of underexplored uncertainties. Uncertain effects associated with CTC include potential long-term sequelae from radiation exposure and potential sequelae from the workup of incidental findings.[15]

CTC examines the entire abdomen, pelvis[3], and sometimes the lower thorax[16] allowing the demonstration of both luminal and extraluminal structures. Some have suggested that detection of nontargeted findings is an advantage.[17, 18] Serracino-Inglott et al concluded that "CT colonography has good patient compliance and is a useful diagnostic modality in detecting colorectal neoplasms. Its main advantage over other such investivgative tools is its ability to detect extracolonic pathology."[18]

Pickhardt and colleagues, however, have described the ability to detect incidental findings as "a potential double-edged sword."[19] While detection does confer the potential benefits of reassurance and discovery of significant treatable pathology at early presymptomatic phases, it carries much potential harm. These potential harms include incidental findings with associated anxiety and unnecessary workup. Diagnostic tests carry risks.[20] These further workups, sometimes invasive, are often costly and may

result in iatrogenic morbidity.[21] With consideration of the potential benefits and potential harms in light of the epidemiology of disease in low-risk groups, it is important to keep an elementary question in the forefront of our thoughts – does CTC produce more benefit than harm?

The economic impact of a widespread CTC screening program remains uncertain for two chief reasons. First, we can only hypothesize the effect that such a program will have on adherence to screening recommendations. While improved adherence to colon cancer screening will confer health benefits, an unexpected extreme improvement may present a great economic challenge. Second, we do not yet know how to handle extracolonic findings (ECFs) appropriately.

Importance

CTC is a rapidly developing practice[21] that has a potential future role in screening for colorectal cancer.[22] Incidental ECFs in CTC are a challenge, however. Applied as a widespread screening modality, CTC screening carries the inevitable responsibility of handling a large number of incidental findings. The accuracy of CTC in detecting luminal lesions has undergone considerable evaluation; however the issue of how to handle the incidental findings is limited and requires further analysis.[23]

In 2002, the USPSTF stated that there was insufficient evidence to recommend for or against CTC as one of the screening modalities. A 2008 guideline released by a joint committee consisting of the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology incorporate CTC as an option for asymptomatic colorectal cancer screening.[24] However, in the 2009

USPSTF update, the Task Force stated that it is still too early to include it in screening recommendations. In February of 2009, the Centers for Medicare and Medicaid Services (CMS) issued a proposed national coverage decision memorandum not to reimburse for CTC for screening purposes.[25] Among other grounds, this memorandum includes the uncertainty of ECFs, stating "Since extracolonic findings are common, evidence based standards and guidelines on reporting, monitoring and subsequent evaluation of these findings are needed."[25]

Clarification of how frequently incidental findings occur, how best to investigate them, and a fuller understanding of the consequences of their detection are necessary to appropriately evaluate the benefits and risks of CTC screening. A comprehensive evaluation of the frequency and consequences – both benefits and drawbacks – of the detection of incidental findings should play a significant role when comparing these modalities to other screening methods for large scale screening programs.[4] This paper will not direct its concern to the overall utility of CTC screening, but will focus on the consequences of further investigation of incidental findings. The objective of this review is to assess the clinical consequences – the benefits, risks, and fiscal impact – of pursuing nontargeted unanticipated findings from CT colonography screening for colorectal cancer.

Methods

The objective of this review is to assess the clinical consequences of pursuing nontargeted unanticipated findings from CT colonography screening. A more thorough understanding of how to handle these incidental findings along with the consequences of their detection is necessary for a more comprehensive analysis of the benefits and harms of large scale screening programs. Identification of incidental findings has served as an adjunct selling point for advocates of these screening methods[17, 18] despite a lack of evidence that their detection affords more benefit than harm. Previous reviews[3, 5, 26] have assessed further investigations of incidental findings found in both asymptomatic and symptomatic patients for these screening modalities. This review is not intended to comprehensively evaluate the consequences of incidental findings for these imaging modalities, but is meant to be analyzed for asymptomatic populations who are described recommended populations for screening tests.

Inclusion and Exclusion Criteria

Prior to probing data, I generated a list of inclusion and exclusion criteria (Table 1). Only studies with a clearly defined population were used. In an attempt to strengthen external validity for screening assessments, I used target populations that are comparable to populations that these large scale screening programs would target. For this reason I included asymptomatic individuals and excluded symptomatic individuals from the targeted population as testing in symptomatic populations would be categorized as diagnostic evaluation rather than screening. I included individuals at normal risk for

colorectal cancer and excluded individuals at increased risk; this includes patients with inflammatory bowel disease, a personal or family history of colorectal cancer or colorectal polyps, and genetic syndromes such as familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer.[27] I excluded studies that included only frail elderly populations. The prevalence of extracolonic findings in this elderly population might be expected to be increased partly due to age alone, but also because the clinical presentations of many conditions are often non-specific in this age group.[23]

I limited the outcome to those studies that included data on further workup of incidental findings. Research designs included primary clinical studies and systematic reviews, studies of more than 100 consecutive research subjects, and studies with methods or results sections defining significant incidental findings. I excluded case control studies because these may overestimate the scale of consequences as a design-related source of bias. I considered only technologies that used a multidetector scanner, necessary to produce images of the colon without gaps.

Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Population	○ Clearly defined population ○ Asymptomatic patients at average risk for colorectal cancer ○ No gender limits ○ No limits on region ○ consecutive subjects	○ Symptomatic patients ○ Populations at high risk for colorectal cancer* ○ Studies dealing specifically with the frail elderly**
Setting	○ CT used for screening of colorectal cancer	○ CT used for diagnostic purposes ○ PET scans and other diagnostic imaging modalities
Date & language	○ 1996 to present ○ English only	
Outcome	○ All incidental findings with analysis of further workup	○ False positives ○ Overdetection
Research design	○ Randomized controlled trials ○ Quasi-experimental studies (including non-randomized controlled studies) ○ systematic reviews ○ cohort studies ○ cross-sectional studies	○ Case series ○ case-control ○ case reports

* Risk factors for colorectal cancer include inflammatory bowel disease, a personal or family history of colorectal cancer or colorectal polyps, and genetic syndromes such as familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer [27]

** Studies were only excluded if they dealt specifically with the frail elderly. Exclusion of this population was not a criterion for study inclusion.

Literature Search and Retrieval Process

Databases and Search Terms

I identified studies by searching electronic databases including PubMed, Embase/Ovid Direct, ScienceDirect, and the Cochrane Database. I included articles from 1996 to present that were available in English only. I included primary clinical studies that included data of follow-ups. I identified three systematic reviews that addressed the consequences of incidental extracolonic lesions on CTC. [3, 5, 26] Details of search terms, strategies, and results are illustrated in detail in table 2 and table 3.

Table 2. Medline search terms, strategies, and results

#1	Incidental findings	4360
#2	Incidental discoveries	4370
#3	Incidental lesions	1565
#4	Extracolonic findings	474
#5	Extracolonic lesions	120
#6	#1 OR #2 OR #3 OR #4 OR #5	5665
#7	Colonography, Computed Tomographic	983
#8	CT colonography	1110
#9	Colonography	1229
#10	Virtual colonoscopy	1242
#11	Colography	27
#12	CT colonoscopy	1088
#13	CT pneumocolon	14
#14	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	2049
#15	#6 AND #14	**82**

Table 3. Results from other electronic databases

Databases	Additional Results
ISI Web of Knowledge	64
EMBASE/OVID	2
ScienceDirect	0
Cochrane database	0

Article selection & review

I conducted the study selection in two stages. I performed an initial screening of titles and abstracts against the inclusion criteria to identify potentially relevant papers. I subsequently screened the full papers that I identified as possibly relevant from the first screening. I examined titles and abstracts and selected those that mentioned evaluating further workup of incidental findings for CTC. I evaluated abstracts for inclusion or exclusion and obtained the full texts of all articles that had potential to be included in the review. I independently reviewed the abstracts and full texts. Double review, though desirable, is not feasible for the purposes of this independent project. I exported the retrieved references to the Reference Manager – Ref Works.

Evaluation of Quality

I critically appraised and quality-rated all of the included studies using criteria modified from those recommended by the USPSTF (Table 4). I appraised studies and gave them a grade of good, fair, or poor based on their overall internal and external validity. Poor quality studies were excluded. I independently appraised quality of the studies; quality was not double reviewed due to the independent nature of this project.

Table 4. Quality appraisal

Citation	Study question & research design	Study population	No endpoint data	Potential for selection bias	Measurement instruments and techniques
Potential for measurement bias	Potential confounders	Potential for confounding	Overall judgment of internal validity	External validity	Comments

Data Extraction

Eligible studies reported on the consequences of following up incidental findings in CTC in asymptomatic average risk populations. I used standardized data collection forms (Tables 5 and 6) for data extraction. I first collected methodological information – including population description and study design information. I subsequently extracted pertinent data from each study into standard tables. The descriptive table (Table 5) illustrates the study question, number and description of participants, method of selection, and endpoint data. The ECF results table (Table 6) illustrates data regarding the prevalence of ECFs, data regarding further investigations, final diagnoses, and costs. Although double data extraction generates fewer errors than single data extraction in

systematic reviews[28], single review was used due to the independent nature of this project.

Table 5. Descriptive

Reference	Study Question	Number of Participants	Description of participants	Method of participant selection	Endpoint data

Table 6. Prevalence of ECFs

Author	Age range	Mean duration of f/u (Interval between CT & last f/u check)	Referral Process	Findings (stratified)	Additional investigations	Important diagnoses made by f/u (and # of pts who derived clinical benefit)	Estimate of additional cost	comments

Data Synthesis

I performed a data synthesis that attempts to answer the following key questions:

- Key Question #1: What is the prevalence of all incidental findings detected on CTC?
- Key Question #2: What is the prevalence of specific types of incidental findings?
- Key Question #3: What are the beneficial outcomes of detecting and investigating incidental findings?
- Key Question #4: What are the harms of detecting and investigating incidental findings?
- Key Question #5: What are the costs and cost-effectiveness of detection and further investigating incidental findings?

I addressed these key questions quantitatively where possible. I addressed these key questions descriptively when quantitative assessment was not feasible.

Results

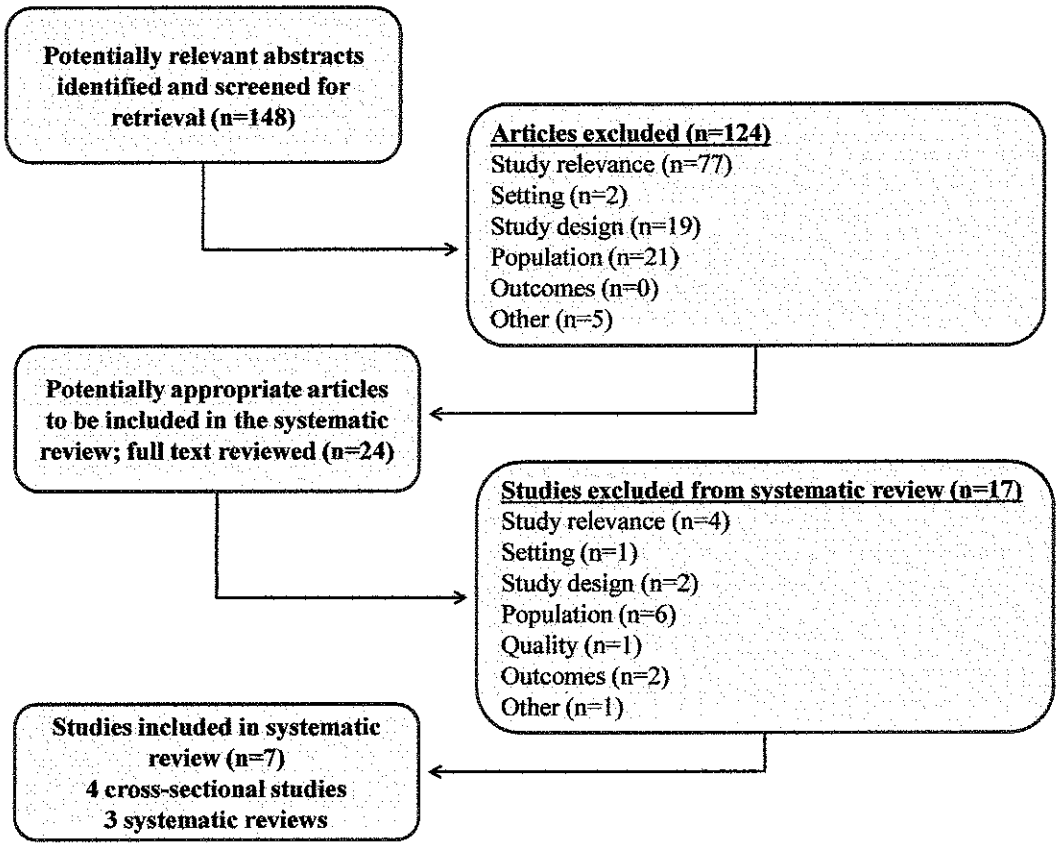
Literature Review

In total, I evaluated 148 abstracts and 24 full-text articles (search results are illustrated in Table 7. I identified 6 primary studies[11, 13, 16, 19, 29, 30] and 3 systematic reviews[3, 5, 26] that addressed the consequences of investigating extracolonic findings detected on screening CTC in average-risk asymptomatic persons from the Medline search. No additional studies from the other databases were included for the review.

I excluded one of the 6 primary studies[30] because it was poor in quality. This study possessed a substantial potential for confounding as nearly two-thirds (61.2%) of the population in this study were high risk with either symptoms or a personal or family history of colorectal polyps or cancer. This study was also limited to men, weakening its external validity. Two papers[11, 19] from the same lead author originated from the same center. The most recent paper[11] did not make it clear whether the two datasets overlapped. I therefore contacted the lead author, who confirmed that the first paper did contaminate the second. I excluded the earlier paper and did not include it in Table 8.

I describe the features of 4 primary studies that met descriptive and quality criteria. All of the studies were of cross-sectional design and defined the primary goal of evaluating extracolonic findings detected on screening CTC in asymptomatic patients. One study[13] examined clinical implications of ECFs with use of IV contrast-enhanced CTC.

Table 7. QUORUM



Quality

Quality ratings are depicted in table 8 (A more complete table is illustrated in Appendix 1. There were no studies with good internal validity. I rated the quality of all four of the included studies as fair. The main source of bias common to all included studies was a short duration of follow-up.

Kimberly et al.[16] reported no endpoint data for 7 of the 143 (4.9%) patients due to insufficient EMR information, producing potential selection bias. The authors contacted subjects' primary care physicians (PCP) if follow-up was recommended but not confirmed on medical records, however they did not contact the PCP in the absence of

medical record confirmation for patients in whom follow-up was not recommended; this produced potential measurement bias. Further potential measurement bias was produced by imaging protocol that included two serial CTCs. Although the authors defined their patient population as asymptomatic, they later reported that symptoms existed in 14 percent (19/136) of patients, producing a potential confounder.

Pickhardt et al.[11] defined their patient population as asymptomatic, but did not specify exclusion criteria. This potential selection bias may have resulted in potential contamination with high-risk subjects.

Kim et al.[13] likewise did not specify exclusion criteria, producing a potential selection bias by potential contamination with high-risk subjects. The authors studied ECFs found with IV contrast-enhanced CT. This may serve as a potential source of measurement bias by altering the frequency and type of ECFs found, and also by altering the frequency of additional investigations of certain ECFs. Use of IV contrast-enhanced CTC is further discussed in the discussion section. External validity of this study is weakened because it was performed in Seoul, South Korea. Despite this study's weaknesses, I decided to include it because it also possesses a number of strengths. First, this study has a larger patient population than any of the other included studies; excluding this study would decrease the total population of the systematic review by 44.7%. Second, while IV contrast-enhanced CT may serve as a potential source of measurement bias, this protocol may, in due course, become a standard measurement. Because of this very possible scenario, this study possesses a unique potential strength with in terms of both measurement and external validity.

All of the studies were geographically limited to either one hospital[11, 16] or to a country outside of the United States.[13, 29] These limitations decrease the generalizability of each study's results to the general population.

Table 8. Description of Studies

Reference	Study Question	Number of Participants	Description of participants	# of ECFs (Total)	# of patients with at least one ECF	Mean duration of follow-up (Interval between initial CT & last follow-up check)	Drop outs (no endpoint data)	Quality Rating
Kimberly	Evaluation of extracolonic findings	136 (data available) out of 143 (enrolled)	Average-risk men and women	423 (3.1 findings per patient screened)	134 (98.5%)	Median: 38 months (mean not reported) Range: 26-45 months	7/143 (not enough EMR info)	Fair
Pickhardt	Evaluation of extracolonic findings	2195	Average-risk or high-risk men and women*	unspecified	unspecified	Mean: 544 days Range: 190-716 days	No loss to follow-up	Fair
Kim	Evaluation of extracolonic findings using IV contrast	2230	Average-risk or high-risk men and women*	2186 (0.98 findings per patient screened)	1484 (66.5%)	Mean: 1.6 years Range:1-3 years	No loss to follow-up	Fair
Chin	Evaluation of extracolonic findings	432	Average-risk men and women	146 (0.3 findings per patient screened)	118 (27.3%)	2 years (defined in protocol)	No loss to follow-up	Fair
Total		4993		At least 2755 (0.56 findings per patient screened)**	1736 (62.0%) (1736/2798)**			

*Exclusion criteria were not specified
**Calculated using total population excluding Pickhardt et al.

Statistical Results

My presentation of results is arranged in accordance to the 5 key questions presented in the methods section. Specifically, I address the following issues:

- Key Question #1: What is the prevalence of incidental findings detected on CTC?
- Key Question #2: What is the prevalence of specific types of incidental findings?

- Key Question #3: What are the beneficial outcomes of detecting and investigating incidental findings?
- Key Question #4: What are harms of detecting and investigating incidental findings?
- Key Question #5: What are the costs and cost-effectiveness of detection and further investigating incidental findings?

Key Question #1: Prevalence of Incidental Findings

Included studies report total number of ECFs from 0.3 to 3.1 per patient with at least one ECF found in 62.0% of screened patients (Table 9). Findings that were recommended or suggested for additional investigation were found in 470 out of the pooled 4993 subjects (9.4%). 297 (5.9%) of all screened patients received additional investigation with studies reporting from 4.5-24%. All of the studies excluded previously known lesions and findings of previously known conditions from final analysis.

Kimberly et al. reported 423 ECFs in 134 patients. Possible explanations for this outstanding number of ECFs are further discussed in the discussion section. Of these, 17.5% were categorized as findings of high importance, 24.5% were findings of moderate importance, and 51.7% were findings of low importance. Thirty-two (24%) patients received additional investigation.

Pickhardt et al. did not report the total number of ECFs. They reported ECFs of at least moderate potential clinical importance in 189 of the 2195 (8.6%) subjects that they observed. Of these, 157 patients (7.2% of the study's population) were recommended or suggested for further investigation because CT findings were sufficient for diagnoses in

32 patients. The deciding primary care physicians pursued further investigations in 133 of subjects (6.1% of the study population), 115 for whom investigations were recommended or suggested and 18 for whom investigations were not recommended or suggested.

Kim et al. used a protocol that utilized IV contrast-enhancement. The study reported 2186 ECFs in 1484 of the 2230 (66.5%) subjects that they observed. Of these, 115 "potentially important" findings were reported in 115 patients (5.2% of the study population). Potentially important findings were defined as "those which required immediate or further diagnostic studies or medical and/or surgical treatment." Further investigations were pursued in 100 of these 115 patients (4.5% of study population) because CTC imaging was sufficient for diagnoses in 15 patients. No further investigations were carried out in other patients. This study reported a lower frequency of patients receiving additional investigation than any of the other studies.

Chin et al. reported 146 ECFs in 118 of the 432 (27.3%) patients that they observed. Of these, 32 "clinically relevant" findings were reported in 32 patients. ECFs were defined as clinically relevant if they "required medical or surgical attention, or further hematological, biochemical, and/or radiological investigation after assessment." All of these 32 patients were further investigated. No further investigations were carried out in other patients.

Protocols of the included studies define methods of referring patients for further investigation that can be placed in two major categories. The studies conducted by Kim et al. and Chin et al. defined protocols that allowed the radiologists to directly refer patients for further investigations. In the studies conducted by Kimberley et al. and

Pickhardt et al., in contrast, radiologists recommended or suggested further investigations to the patients' primary care physicians who were the ultimate decision-makers. In these two studies, there is an important lack of correlation between findings deemed important by radiologists upon detection and those that receive further investigation. Both the Kimberly and Pickhardt studies report a significant number of findings of high importance and findings of moderate importance that underwent no additional evaluation (Table 9). Both studies also reported a considerable number of findings that underwent further evaluation without radiologist recommendation or suggestion. Only one of the studies[11] addressed findings that were pursued by the referring physician in the absence of radiologist recommendation. These authors reported that "no clinically important diagnoses" were established in any of these patients. The authors neither defined clinically important diagnoses nor described how they were determined.

Table 9. Radiologic Importance versus Actual Further Investigation

Author	ECFs	Findings (stratified)	Received Additional workup	% of additional workup in each strata
Kimberly	423 ECFs in 134 of 136 (98.5%) patients	High* – 25 ECFs in 25 patients (17.5% of study population) Moderate* – 53 ECFs in 35 patients (24.5% of study population) Low – 345 ECFs in 74 patients (51.7% of study population)	Total – 32 patients (24% of study population) High = 14/25 (56%) Moderate = 15/35 (43%) Low = 3/74 (4%)	44% = High importance 47% = Moderate importance 9% = Low importance
Pickhardt	unspecified	Moderate to High – 189 patients (8.6% of study population) Note: 157 patients (7.2% of study population) suggested or recommended because for 32 patients, CT findings were sufficient for diagnosis	Total - 133 patients (6.1% of study populatio) Recommended or suggested = 115 pts Not recommended or suggested = 18 pts	High/Moderate = 86% Low = 14%
Kim	2186 ECFs in 1484 of 2230 patients (66.5% of study population)	"Potentially Important"* – 115 ECFs in 115patients (5.2% of study population)	Total - 100 patients (4.5% of study population) Note: 15 pts, CT findings were sufficient for dx	All additional work-up was conducted in clinically relevant strata as per protocol
Chin	146 ECFs in 118 of 432 patients (27.3% of study population)	"Clinically Relevant"* – 32 ECFs in 32 patients (7.4% of study population)	Total - 32 patients (7.4% of study population)	All additional work-up was conducted in clinically relevant strata as per protocol

*Recommended or suggested for additional investigation by radiologist
**May include previously known lesions

Key Question #2: Prevalence of Specific Types of Incidental Findings

A number of different pathologies were ultimately diagnosed, and many treated, subsequent to CTC detection. The findings illustrated in Table 10 represent only the common mentioned findings in two of the studies.[11, 13] The other studies[16, 29] did not report the specific types of findings that were ultimately diagnosed or treated following complete work-up. The most common diagnosed pathologies that were reported in the

two studies were nonmalignant tumors (at least 1.5% of those screened in the two studies), malignant tumors (0.5% of those screened in the two studies) and aortoiliac aneurysms (0.3% of those screened in the two studies). A more detailed description of specific types of findings is illustrated in Table 10.

Table 10. Prevalence of specific types of findings

Finding	Number	% of screened subjects (4425 subjects)*
Nonmalignant tumors	at least 68	At least 1.5%
1. Adrenal gland mass	42†	At least 0.9%
2. Benign ovarian tumor**	15	3.5%
3. Retroperitoneal neurogenic tumor	1	0.02%
4. Pancreatic solid and papillary neoplasm	2†	At least 0.05%
5. Benign hepatic mass	3†	At least 0.07%
6. Benign renal mass	3†	At least 0.07%
7. Benign prostate mass	2†	At least 0.05%
Malignant tumor	23	0.5%
1. Non-Hodgkin lymphoma	3	0.07%
2. Renal cell carcinoma	8	0.2%
3. Abdominal metastatic disease	2	0.05%
4. Bronchogenic carcinoma	2	0.05%
5. Cervical	1	0.02%
6. Gastric adenocarcinoma	1	0.02%
7. Hepatocellular carcinoma	3	0.07%
8. Pancreatic adenocarcinoma	1	0.02%
9. Gastrointestinal Stromal Tumors (GIST)	2†	At least 0.05%
Aortoiliac aneurysm	14	0.3%
Urolithiasis	6	0.14%
Hepatic eosinophilic abscess	4†	At least 0.09%
Pneumonia	4†	At least 0.09%
Pulmonary ground glass opacity (GGO)	4†	At least 0.09%
Pancreatic IPMT	4†	At least 0.09%
Congenital renal anomaly	4†	At least 0.09%
Porcelain gallbladder	3	0.07%
Liver cirrhosis	3†	At least 0.07%
Tuberculosis	2†	At least 0.05%
Splenomegaly	2†	At least 0.05%
Benign enlargement of uterus	2†	At least 0.05%
Mucinous adenoma of appendix	2†	At least 0.05%
Endometriosis	2†	At least 0.05%

*these calculations consider only pooled populations in Pickhardt et al. and Kim et al. (n=4425)
**mucinous or serous cystadenomas or cystadenofibromas (n=7) and benign teratomas (n=8)
†Mentioned by either Kim et. al. or by Pickhardt et al., but not both

Key Question #3: Benefits of Detection and Investigation

A number of potential benefits may have resulted from the detection and investigation of incidental findings. The studies do not report the information necessary

to report accurate quantitative data. Some of the studies do, however, describe some specific examples of investigations that led to a number of pathologies that were diagnosed and treated. While diagnoses and treatments these findings may be of potential benefit, the studies provide no information regarding the ultimate outcomes. Thus we cannot presume that the mentioned diagnoses or treatments resulted in advantageous outcomes.

Kim et al. reported 12 malignant tumors (Table 11). Eleven of these 12 extracolonic tumors underwent surgical resection. One (cervical cancer) was treated with radiation therapy. In the same report, 2 aldosterone-producing adenomas and 4 ovarian masses were treated surgically. Pickhardt et al. reported that new diagnoses "of at least moderate clinical importance" were found in 55% of patients (2.5% of screened patients). The authors neither define "moderate clinical importance" nor describe how these diagnoses were generated. Kimberly et al. reported that one subject who was diagnosed with an asymptomatic noninvasive renal cell cancer is likely to have benefited in terms of mortality. This study also reported that one patient with large asymptomatic bladder stones was referred to a urologist and eventually underwent cystoscopy. The patient received a transurethral dilation of the prostate and a urethral dilation to facilitate passage of these stones.

At least 114 patients (2.3% of screened patients) received a clinical diagnosis with studies reporting from 1.9% to 2.5% (Table 11). At least 46 patients (0.9% of screened patients) underwent treatment, with individual studies reporting up to 2.0%. These diagnosed and treated findings may or may not be of true benefit. The true benefit of pursuing findings is unlikely to include all of the diagnosed and treated pathologies.

Table 11: Patients with Potential Clinical Benefit

Author	Patients with Additional investigation	% of study population undergoing further investigation	# of patients who received diagnoses	% of all subjects who received diagnoses*	Total # of patients who received treatment	% of all subjects who received treatment*
Kimberly	32	24%	Not reported	?	At least 1	?
Pickhardt	133	6.1%	55	2.5%	Not reported	?
Kim	100	4.5%	51	2.3%	45	2.0%
Chin	32	7.4%	8	1.9%	Not reported	?
Total	297	5.9%*	At least 114	At least 2.3%*	At least 46	At least 0.9%*

* calculated using the total number of subjects (n=4993)

Key Question #4: Harms of Detection and Investigation

Further investigation resulted in a number of further radiological assessments, many of which revealed findings of benign nature. For example, Pickhardt et al. reported that all 10 patients who underwent subsequent contrast-enhanced CT or MR imaging for indeterminate liver lesions were found to have benign cavernous hemangiomas of no clinical importance.

Seventy-five subjects (1.5% of screened patients) received surgical or medical procedures, with studies reporting frequencies from 0 to 3.7% (Table 13). None of the studies report the comprehensive information necessary to report accurate quantitative values regarding the frequency of avoidable procedures. Some of the studies, do however, report specific examples of procedures that led to benign diagnoses. Pickhardt et al. reported 10 women (0.8% of all women screened) who underwent laparoscopic resection for complex ovarian lesions; all of which proved to be benign neoplasms. Although 1 bronchogenic carcinoma was found and later excised (as previously described in KQ#3), 3 CT-guided biopsies and 1 thoracoscopic resection resulted in 3 benign diagnoses. Kim et al. reported 2 benign schwannomas diagnosed by surgery. Kimberly et al. reported a total of 5 medical procedures, 4 of which proved benign diagnoses.

These authors reported 2 upper endoscopies for esophageal or gastric thickening; both revealed no abnormalities. One fiberoptic bronchoscopy with transbronchial lung biopsy and cultures yielded revealed no abnormality. One patient with an adnexal mass received a laparoscopic oophorectomy which was diagnosed as a benign ovarian cyst.

Adverse effects including infection, hemorrhage, cardiovascular complications, and mortality are examples of known problems associated with invasive procedures.[31] A number of factors influence the frequencies of these adverse effects making it difficult to estimate the expected frequencies of particular adverse effects that may arise with the implementation of widespread screening. None of the studies reported data on such adverse effects associated with these procedures. Various other types of harms, such as psychological impact and lost time from work, were not acknowledged in these studies. The only mention of potential harm in any of the included studies was provided by Pickhardt et al. who reported that no "important complications" resulted from any additional workup.[11] The authors offered no definition of "important complications" in the report.

A comprehensive analysis on the harms of detecting ECFs is difficult to obtain from these studies. Considering reported data from Chin et al. and extrapolated numbers from Pickhardt et al. and Kim et al. (this information could not be extrapolated from Kimberly et al.), an average of 3.1 percent of the screened population (excluding those screened in Kimberly et al.) received additional investigation that resulted in no reported diagnosis (Table 12). Extrapolated values were obtained by subtracting the number of subjects who received reported (Table 11) from the number of patients who underwent

investigation. 0.5% of screened subjects (not including subjects in Pickhardt et al.) received an invasive procedure that resulted in benign diagnoses.

These extrapolated values should be interpreted with caution. Because the percentage of patients who received reported diagnoses represents a minimum number, these extrapolated values overestimate the true number of subjects who received further investigation with no reported diagnoses. The true number of subjects who received further investigation with no reported diagnosis underestimates the number of subjects who received clinical harm with no clinical benefit. Since a certain percentage of those who received reported diagnoses ultimately receive no clinical benefit, the number of patients receiving harm is greater than the true number of subjects who received further investigation with no reported diagnoses. The numbers of further investigations and invasive procedures that result in no reported diagnoses should furthermore be interpreted in a different manner than those that describe potential benefits. All of the patients who received further investigations with no diagnoses or treatment experienced at least some degree of anxiety or lost time that would have been avoided if the findings had not been detected. All of the patients who received invasive procedures likewise experienced at least some degree of pain, anxiety, and lost time.

Table 12. Additional investigations resulting in no clinically important diagnoses

Author	Patients with Additional investigation	# of patients who received additional workup with no reported diagnoses	% of study population who received additional workup with no reported diagnoses
Kimberly	32	?	?
Pickhardt	133	78*	3.6%*
Kim	100	49*	2.2%*
Chin	32	24	5.6%
Total	297	151**	3.1%**

*These numbers were not reported in the studies but were obtained by subtracting the number of patients who received clinically important diagnoses or treatment (see Table 11) from the number of patients with additional investigation

**These numbers considered the data included in Pickhardt it al., Kim et al., and Chin et al. but not Kimberly et al. (n=4859)

Table 13. Invasive procedures resulting in benign findings

Author	# of invasive procedures	% of study population receiving procedures	# of invasive procedures resulting in benign findings	% of invasive procedures resulting in benign findings	% of study population who received an invasive procedure with benign finding	Major harms reported
Kimberly	5	3.7%	4-5*	80-100%	2.9-3.7%	?
Pickhardt	41	1.8%	?	?	?	0
Kim	29	1.3%	9**	31.0%	0.4%	?
Chin	0	0%	0	N/A	0	?
Total	75	1.5%	At least 13**	38.2%***	0.5%†	?

*one procedure aided passage of an asymptomatic bladder stone that had the potential to cause symptoms down the road

**It is difficult to assess whether or not some procedures are necessary or unnecessary.

***These numbers did not consider data from Pickhardt et al. (denominator = 34 invasive procedures)

† These numbers did not consider data from Pickhardt et al. (n=2798)

Key Question #5: Costs and Cost-effectiveness of Detection and Further Investigation

Cost estimates from the Kim, Chin, and Pickhardt studies underestimate the true cost of further investigation. Kim et al calculated only imaging costs (Table 14). Chin et al reported no procedures in their results; a larger study population would likely have led to a number of performed procedures which would have heavily influenced the calculated cost.

True cost estimates of additional workup likely fall between $98.56 (reported by Pickhardt et al.) and $248 (reported by Kimberly et al.) per person screened. The

calculation reported by Pickhardt et al is based on a large population but does not include costs of referrals and return visits, therefore likely underestimating the true cost. Costs calculated by Kimberly et al. reflects additional radiographic studies, laboratory studies, medical procedures, referrals and return visits that resulted solely from ECFs. Assuming that the estimate provided by Pickhardt et al. is a reasonably accurate reflection of costs without referrals and return visits, it is unlikely that referrals and return visits are responsible for the 60% difference in cost reported by Kimberly et al. Therefore this small-scale study may have overestimated the true cost.

A cost-effectiveness analysis cannot be properly performed without a more thorough understanding of the true benefits and harms.

Table 14. Costs

Author	Additional cost of investigating ECFs (per patient screened)	Country	Included in cost analysis
Kimberly	$248	United States	Radiological studies, laboratory studies, medical procedures, referrals & return visits
Pickhardt	$98.56	United States	Radiological studies, laboratory studies, medical procedures
Kim	$2.34	Korea	Radiological studies only
Chin	$24.37	Australia	Radiological studies, laboratory studies, clinical evaluation

Synthesis of Evidence

At least one newly found ECF was detected in 62.0% of screened patients (KQ#1). Many differences existed between the studies, including differences in categorization of importance, varying measurement protocols, and differences in referral methods. 297 patients (5.9% of the total screened population) received additional investigations.

The most common diagnosed pathologies (KQ #2) are nonmalignant tumors, which occurred in at least 1.5% of screened patients. Malignant tumors were diagnosed in 0.5% of screened patients, and aortoiliac aneurysms were diagnosed in 0.3% of screened patients.

The true benefits of detecting incidental findings (KQ#3) remain unclear. The studies provide no information regarding the ultimate outcomes. At least 2.3% of screened patients received a clinical diagnosis and at least 0.9% of screened patients underwent treatment. The true benefit of detecting and pursuing findings is unlikely to include all of the diagnosed and treated pathologies.

An accurate report of the adverse effects (KQ#4) is difficult to interpret from these studies. The included studies made little to no mention regarding adverse effects. A number of patients received additional imaging and invasive procedures. An average of 3.1% of screened patients received additional investigation that resulted in no reported diagnosis. This value may overestimate the true number of additional investigations that resulted in no reported diagnoses. 0.5% of screened subjects received an invasive procedure that resulted in benign diagnoses. The true numbers of patients who received no reported diagnoses after further investigations represent the minimum number of patients who received at least some degree of harm with no benefit.

The cost of pursuing incidental findings (KQ#5) likely falls between $98.56 and $248. Cost-effectiveness analysis cannot be assessed without a more comprehensive evaluation of the benefits and harms.

Discussion

Major Findings

I found no randomized trials that evaluated the consequences of investigating extracolonic findings on CTC screening. I therefore evaluated the available literature with five key questions that focused on the prevalence, benefits, harms, and costs of their detection and follow-up.

Incidental lesions were found in 62% of screened patients and 5.9% of the total screened population received additional investigations. The number of incidental findings varied between studies. Kimberly et al. reported a much higher frequency of ECFs than did the other studies. The authors attributed this difference to a measurement protocol that included the use of 2 CTCs serially and a protocol that did not minimize visualized lung parenchyma. The local training and practices of the radiologists influenced which findings warranted being reported. For example, degenerative disease of the spine was the second most common finding in Kimberly et al., whereas this finding wasn't reported in any subjects in other studies. Differences in reporting may significantly alter the frequency of findings. These effects are particularly manifested given that each of the studies was performed in one to two centers.

The frequency of detection was not a strong predictor of either additional pursued investigation. For instance, though Kim et al. reported over two times the frequency of patients with ECFs as Chin et al. (66.5% and 27.3%, respectively), they reported a lower frequency of additional investigation per patient (4.5% and 7.4%, respectively). One important factor contributing to the lack of correlation is differences in referral practices. Protocols used by Kim et al. and Chin et al. gave final decision-making responsibility to

radiologists whereas protocols used by Kimberly et al. and Pickhardt et al. gave the final responsibility to the patients' primary care physicians. Furthermore, data from the studies that gave decision-making responsibility to the primary care physicians demonstrated a low correlation between those deemed important by the radiologist and those that the primary care physician selected to investigate.

Kim et al. studied ECFs with the use of IV contrast-enhancement, claiming that it is harder to characterize lesions without contrast material, which leads to unnecessary further evaluation. IV contrast-enhancement improves the specificity, conveys greater information than non-contrast exams,[26] and enables the radiologist to distinguish between solid and cystic lesions.[13] This method may permit identification and characterization of additional unexpected abnormalities.[32, 33] Use of IV contrast decreases the percentage of poorly defined lesions and increases the number of complete diagnosed lesions – yielding more clear diagnoses. Therefore, use of IV contrast may decrease the number of further investigations by reducing incompletely characterized lesions.[11, 13, 35] The frequency of patients with at least one ECF was 66.5%, comparable with the average of all of the included studies (62.0% of screened subjects). The frequency of patients receiving additional investigation (4.5% of screened subjects) is lower than that of any of the other studies included in this review. While decreased frequency of additional investigations may be a potential benefit of IV contrast-enhancement, it also includes potential limitations such as additional costs, longer time, invasiveness, higher radiation dose, and increased risk of adverse reactions to contrast agents.[32]

The overall benefit of detecting incidental findings remains unclear, mainly because none of the studies provide information regarding ultimate outcomes. At least

2.3% of screened patients received a clinical diagnosis and at least 0.9% of screened patients underwent treatment. The true benefit of detecting and pursuing findings is likely to include some, but not all, of the diagnosed and treated pathologies.

While the included studies made little mention regarding adverse effects, it is clear that a number of patients experienced at least some degree of harm with no benefit. A number of patients received additional imaging and invasive procedures. Approximately 3.1% of patients received additional investigation that resulted in no reported diagnosis, though this may be an overestimate of the true value. At least 0.5% of screened subjects received an invasive procedure that resulted in benign diagnoses. All patients who receive further investigation with no diagnosis receive at least some degree of harm.

Comparison to Past Relevant Studies

I located three systematic reviews that address the consequences of following up ECFs incidentally found on CT colonography.[3, 5, 26] These reviews focused largely on prevalence of nature of the findings. None of these systematic reviews reported data regarding harm or investigations that resulted in benign findings.

A 2005 systematic review conducted by Xiong et al.[3] examined 9 studies that examined the nature and frequency of incidental findings on CTC. The frequency of screened patients with incidental findings in this review was similar to that of Xiong et al. (62% and 58%, respectively). This review reported a lower frequency of additional investigation than the review conducted by Xiong et al. (5.9% and 13.8% of screened populations, respectively) and a higher number of screened subjects who received

treatment (at least 0.9% and 0.8% of screened subjects, respectively) than in the report by Xiong et al. However, Xiong et al. described these as findings that "needed immediate treatment." The authors did not offer a precise definition of "immediate treatment." The two most common findings were cancer and aortoiliac aneurysms in both this study and that of Xiong et al. (2.4% and 3.7% of screened subjects, respectively, had either cancer or an aortoiliac aneurysm). In contrast to this study, the majority of the studies in included by Xiong et al. used symptomatic patients rather than those with a population risk for colorectal cancer.

In a 2008 systematic review, Siddiki et al.[26] examined the frequency, categorization, and spectrum of incidental findings. The authors reported separate data for symptomatic and asymptomatic populations. The frequency of asymptomatic patients with incidental findings reported by Siddiki et al. was slightly lower than that reported in this review (53% weighted mean and 62% respectively). Siddiki et al. reported similar frequency of ECFs requiring further investigation as this review (5-8% and 5.9% respectively). Siddiki et al. reported 1.3 – 2.3% of asymptomatic screened patients underwent subsequent medical or surgical intervention. Some of the asymptomatic populations included in the Siddiki review[14, 30, 34, 35] include high risk patients and therefore likely overestimate the prevalence and importance of ECFs in an average-risk population.

In a 2008 USPSTF systematic review for colorectal cancer screening, Whitlock et al. [5] reported the frequency of ECFs of high importance (4.5% to 11% in screened subjects), ECFs of moderate clinical significance (up to 27% in screened subjects), and recommended additional evaluation (7% to 16% in screened subjects) in asymptomatic

populations. The report did not investigate the number of patients that underwent further investigation. The authors reported that a minority of those recommended ultimately warranted definitive treatment, though no quantitative value was offered. Many studies in the Whitlock review included high-risk subjects.

Public Health Implications

This systematic review examined the studies with the highest available quality that addressed the average-risk asymptomatic populations that are recommended to receive colorectal cancer screening. The data in this review is insufficient to comprehensively examine benefits and harms and thus adds to the current body of evidence that we do not know how to suitably handle incidental extracolonic CTC findings.

Future Studies

Endorsements for CTC use for screening will be more likely to occur with the minimization of uncertainties (i.e. such as incidental findings), increased cost-effectiveness, and most importantly, evidence of improved ultimate outcomes. An understanding of CTC assessment methodology offers a perspective on how future studies may be performed in a more pragmatic manner that allows us to utilize CTC while minimizing uncertainties and costs by eliminating the visualization of extracolonic findings.

CTC images are reviewed using 2D multiplanar images and 3D endolumenal displays of the colon.[3] The 3D endolumenal ("flythrough") display illustrates the inside

of the colon, as does conventional video colonoscopy (hence the nickname "virtual colonoscopy"). 3D endolumenal displays are assessed separately from the 2D multiplanar images. Assessment of 2D axial images is not necessary for the identification of colon polyps; it is used to examine extralumenal structures and some diffuse colonic diseases.[36] Therefore assessment of 3D endolumenal display only (with the elimination of 2D multiplanar assessment) presents a modality most similar to the gold standard colonoscopy without the visualization incidental findings.

A head-to-head randomized controlled trial (RTC) comparing colonoscopy to 3D endolumenal displays (with the elimination of 2D multiplanar assessment) will give us a more accurate assessment of the value of CTC for the pathology in question – colorectal cancer. The ultimate benefits and harms of interest are numerous, complex, and difficult to extrapolate with prevalence studies. A trial will provide direct data of the desired ultimate outcomes such as mortality reduction. Assessment of 3D endolumenal displays with 2D multiplanar assessment as a third arm can provide valuable preliminary information of the true consequences of pursuing incidental findings.

In addition to eliminating the uncertainties that accompany detection of incidental findings, a trial that examines the assessment exclusively of 3D endolumenal displays may demonstrate improved feasibility for widespread implementation given decreased costs and increased expedience. Furthermore, it has been suggested that the common finding of incidental lesions may lower the utility of CTC. Removing the detection of these findings may therefore improve one of the largest limitations of colorectal cancer screening – adherence.

Examining scans for incidental findings and reporting them represents a non-trivial investment in time, study design, and resources by CTC research teams. Researchers have previously addressed the potential of disregarding extracolonic findings. Some researchers cite the importance of moral and legal obligations to pursue incidental findings, including respect for persons and the researcher's duty to warn of foreseeable harm.[26] Pickhardt et al. state that withholding or not reviewing imaged regions raises clinical and ethical concerns, especially given the potential that a relevant finding is harbored.[11] If a trial does, however, demonstrate a benefit exclusive 3D endolumenal examination over conventional colonoscopy, these ethical and medicolegal obstacles will be challenged.

Defining a standard protocol for pursuing incidental findings will likely prove to be a long and tedious venture. Such an undertaking should be reserved until CTC demonstrates improved outcomes with exclusive use for colorectal pathology.

Strengths and Limitations

A strength that distinguishes this systematic review apart from others is that it studies an average-risk population by excluding studies that examined only symptomatic patients, high-risk patients, and elderly patients. I was unable to locate any other review that exclusively examined an average-risk population.

This review has some limitations. First, the review included a small number of studies and a relatively small patient population. Second, all of these studies were cross-sectional studies and were fair in quality. All of the included studies reported a short duration of follow-up that is responsible for considerable measurement bias. Third, I

limited the search to English-language articles, and therefore I may have excluded studies from similar non-English-speaking populations. Fourth, none of the studies appropriately addressed the harms of CTC.

Conclusions and Summary of Main Findings

Some clinical benefit may arise from pursuing ECFs. Some important pathologies were ultimately detected and many were treated. We cannot conclude that the early detection and treatment of the ECFs during asymptomatic phases confers a benefit over diagnostic evaluation and treatment in later symptomatic phases. This review cannot offer an accurate estimate of true clinical benefit of pursuing ECFs. No studies have evaluated the harms of pursuing ECFs so we likewise cannot calculate an appropriate estimate of the true harm. We do know that a number of additional investigations and procedures were pursued that resulted in benign diagnoses. From these, we can presume that pursuing ECFs produces at least some degree of harm. Importantly, we cannot estimate the varying degrees of benefits and harms. Available studies, therefore, do not bring us closer to settling the central key issue – weighing the overall benefits versus the harms.

CTC screening has the potential to make a significant impact on colorectal cancer screening. Our understanding of how to handle ECFs remains far from where it needs to be if CTC were to become a modality recommended for widespread screening. A trial is therefore warranted to provide a more comprehensive and accurate assessment of the desired ultimate beneficial and harmful outcomes.

Prior to extensive assessment of how to handle incidental findings, we should first perform a basic evaluation of CTC for the pathology in question – precancerous colorectal polyps – in the absence of incidental findings. A trial comparing colonoscopy with the exclusive assessment of 3D endolumenal display CTC will offer the most pertinent data to assess the true ability of CTC to confer a benefit over colonoscopy regarding colorectal cancer.

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Appendix A – Quality Appraisal

Table 1: Quality appraisal of Kimberly et al.

Citation	Study question & research design	Source & Study population	No endpoint data	Potential for selection bias	Measurement instruments and techniques
Kimberly, et al. 2008	Evaluation of extracolonic findings Cross-sectional	Patients at one large university medical center referred for colonoscopy screening. 40 y/o or older. Excluded if high risk or presence of illness precluding participation. 136 patients (of 143 consecutive patients referred for conventional colonoscopy)	7/143 (not enough EMR info)	++ Contacted PCP if follow-up was recommended but not confirmed on medical record; did not contact PCP in the absence of medical record confirmation for patients in whom follow-up was not recommended	Two serial CTCs 5mm collimation PCP pending radiologist recommendation or suggestion Short duration of follow-up
Potential for measurement bias	**Potential confounders**	**Potential for confounding**	**Overall judgment of internal validity**	**External validity**	**Comments**
+++ *	Some elderly patients included some patients reported symptoms at baseline	++	Fair	Fair Study performed at only 1 hospital – radiologist training and hospital-specific protocols may not be generalizable	Costs include imaging, laboratory tests, procedures, and referrals and return visits.

* Short duration of follow-up is responsible for high degree of measurement bias. This unavoidable source of bias will not preclude inclusion of study into the review.

Table 2: Quality appraisal of Pickhardt et al.

Citation	Study question & research design	Source & Study population	No endpoint data	Potential for selection bias	Measurement instruments and techniques
Pickhardt et al. 2008	Evaluation of extracolonic findings Cross-sectional	Asymptomatic patients at one large university medical center referred for colonoscopy screening. 40 y/o or older. Asymptomatic adults. Exclusion criteria not specified. 2195 consecutive patients	No loss to follow-up	++ method of pt selection not described thoroughly	1.25mm collimation PCP pending radiologist recommendation or suggestion Short duration of follow-up
Potential for measurement bias	**Potential confounders**	**Potential for confounding**	**Overall judgment of internal validity**	**External validity**	**Comments**
++ *	Some elderly patients included Possible inclusion of high-risk patients Gender – (54.7% female)	++ to +++	fair	Fair Study performed at only 1 hospital – radiologist training and hospital-specific protocols may not be generalizable	Cost only includes imaging, labs, and procedures. Referrals and return visits not included.

*Short duration of follow-up is responsible for high degree of measurement bias. This unavoidable source of bias will not preclude inclusion of study into the review.

Table 3: Quality appraisal of Kim et al.

Citation	Study question & research design	Source & Study population	No endpoint data	Potential for selection bias	Measurement instruments and techniques
Kim et al. 2007	Evaluation of extracolonic findings using IV contrast Cross-sectional	Asymptomatic patients at one large university medical center referred for colonoscopy screening. 50 y/o or older. Asymptomatic adults. Exclusion criteria not specified. 2230 consecutive patients	No loss to follow-up	++ method of pt selection not described thoroughly	all potentially important findings referred for follow-up by radiologists; those not followed were still monitored and many were followed up later IV-contrast enhanced CT 0.75mm collimation Referral direct from radiologist Short duration of follow-up
Potential for measurement bias	**Potential confounders**	**Potential for confounding**	**Overall judgment of internal validity**	**External validity**	**Comments**
+++ *	Some elderly included Possible inclusion of high-risk patients Gender (60% men)	++ to +++	Fair	Fair/poor Study performed in Seoul, Korea	IV contrast-enhanced CT not excluded because there currently is no gold standard for CTC protocol. Cost data derived from Korean National Health Insurance Act and Enforcement Ordinance and calculated in US dollars at the 2004 basic exchange rate. Cost only includes imaging. Procedures, labs, referrals and return visits not included.

* Short duration of follow-up is responsible for high degree of measurement bias. This unavoidable source of bias will not preclude inclusion of study into the review.

Table 4: Quality appraisal of Chin et al.

Citation	Study question & research design	Source & Study population	No endpoint data	Potential for selection bias	Measurement instruments and techniques
Chin et al. 2005	Evaluation of extracolonic findings Cross-sectional	Asymptomatic participants in two community-based colorectal neoplasia screening programs by CTC; both groups randomly drawn from Australian database. 50 y/o or older. Excluded if high risk or presence of illness precluding participation. 432 consecutive patients	No loss to follow-up	+ well described method of selection	Referral direct from radiologist 5mm collimation; 3mm collimation Short duration of follow-up
Potential for measurement bias	**Potential confounders**	**Potential for confounding**	**Overall judgment of internal validity**	**External validity**	**Comments**
+++ *		+	Fair	Fair Study performed in Austrailia	No procedures were reported in this study; this likely influences cost calculations. Cost does include referrals and return visits.

*Short duration of follow-up is responsible for high degree of measurement bias. This unavoidable source of bias will not preclude inclusion of study into the review.