Meta-analysis Shows Colon Capsule Endoscopy Is Effective in Detecting Colorectal Polyps

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BACKGROUND & AIMS: Colon capsule endoscopy (CCE) is a noninvasive and painless technique used to explore the colon without sedation or air insufflation. We performed a systematic review and meta-analysis to assess the accuracy of CCE in detecting colorectal polyps. **METHODS:** The MEDLINE, EMBASE, and SCOPUS databases were searched, from 2006 to 2009, for the terms "colon capsule" and "Pillcam colon"; searches included abstracts. Studies were included that focused on detecting colorectal polyps with CCE and that were verified using within-subject reference colonoscopy. The risk of bias within each study was ascertained according to Quality Assessment of Diagnostic Accuracy in Systematic Reviews recommendations. The per-patient sensitivity and specificity were calculated for polyps of any size and for significant findings (polyps, ≥6 mm in size or >3 in number). Forest plots were produced based on random-effect models. The risk of bias across studies was assessed using the interstudy heterogeneity statistic, meta-regression, and the Egger test. **RESULTS:** Eight studies provided data on 837 patients; the prevalences of polyps and significant findings were 57% and 27.4%, respectively. CCE sensitivity for polyps of any size and significant findings were 71% and 68%, respectively. CCE specificity for polyps of any size and significant findings were 75% and 82%, respectively. High levels of heterogeneity (interstudy heterogeneity, >75%) were not detected. Moderate heterogeneity partially was explained by the different design of individual studies. CCE identified 16 of the 21 cancerous lesions detected by colonoscopy (pooled sensitivity, 76%). **CONCLUSIONS: CCE sensitivity for polyps and significant findings compares favorably with other noninvasive colorectal cancer screening strategies. CCE specificity is likely to be underestimated because reference colonoscopy examination results are blinded.**

Keywords: PillCam Colon; Colorectal Cancer Screening; Colorectal Cancer; Advanced Neoplasia.

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Colorectal cancer (CRC) represents a major cause of morbidity and mortality in Western countries.[1] Despite the fact that identification and removal of precancerous polyps at colonoscopy has been shown to be effective in preventing CRC,[2] CRC screening uptake is still disappointingly low, especially when compared with breast, cervical, and prostate screening programs.[3,4] To improve acceptability and safety of CRC screening, PillCam Colon Capsule Endoscopy (CCE) (Given Imaging, Ltd., Yoqneam, Israel) has been pioneered.[5–9] CCE represents a noninvasive, painless, swallowed colonoscope that is able to explore the colon without requiring sedation and air insufflation.

The potential efficacy and cost effectiveness of CCE in preventing CRC depend on its accuracy for colorectal lesions, such as polyps or masses.[10] Such accuracy in turn may be related with technical characteristics, such as the quality of the bowel preparation and the ability of CCE to visualize all the colonic mucosa.

For CCE, ambitious claims mostly are based on relatively few within-subject comparisons with colonoscopy from single centers. These studies vary considerably in terms of study design, selected population, and technical performances of the CCE.

The aim of this systematic review and meta-analysis was to assess CCE accuracy as verified with within-subjects colonoscopy in detecting colorectal lesions.

Methods

Methods of the analysis and inclusion criteria were based on Preferred Reporting Items for Systematic Reviews of Meta-Analyses (PRISMA) recommendations.[11]

Eligibility Criteria

All the studies in which subjects at average or increased risk of CRC underwent CCE and complete colonoscopy for verification were considered for inclusion. To be included in our analysis, the focus of the study had to be the detection of colorectal polyps, irrespective of histologic findings. Inclusion criteria also required the construction of 2 × 2 tables. Studies without details of polyps and their verification with colonoscopy were excluded, as well as those with fewer than 10 patients. We did not include review articles, position papers, editorials, commentaries, or book chapters. If there was any suspicion of a duplicate study, the most recent study with the largest cohort was considered for inclusion.

Abbreviations used in this paper: CCE, colon capsule endoscopy; CI, confidence interval; CRC, colorectal cancer; CT, computed tomography; I^2, interstudy heterogeneity; MeSH, Medical Subject Headings; PRISMA, Preferred Reporting Items for Systematic Reviews of Meta-Analyses.

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Information Sources

A literature search was performed in October 2009. Relevant publications were identified by MEDLINE, EMBASE, and SCOPUS for the period from 2006 to 2009 (ie, which to our knowledge is when the technique was first described). The medical terms "colon capsule," "Pillcam colon," "capsule endoscopy," (Medical Subject Headings [MeSH] term) *and* "colon" (MeSH term) were used in the search, without language restrictions. We hand-searched the references of review articles and evaluated symposia proceedings (Digestive Disease Week and United European Gastroenterology Federation). The full article/abstracts of all relevant studies were retrieved, and manual searches of reference lists from identified relevant articles were performed.

Study Selection

Studies were selected based on the title and/or the abstract by 2 researchers (C.S. and C.H.). The reviewers checked whether inclusion and exclusion criteria were met and, in the event of uncertainty, the full text of articles was retrieved and reviewed.

Data Collection Process and List of Items

Data extraction was performed independently using predefined data extraction forms by the 2 reviewers. A third investigator (G.C.) arbitrated in the event of a lack of agreement. From each report, reviewers independently abstracted the following: (1) the year of publication, (2) country where the study was performed; whether it was a (3) single-center or multicenter study, (4) a prospective or retrospective study, (5) abstract or article, (6) number of patients considered for inclusion, (7) number of patients excluded, (8) reasons for exclusion, (9) definition of significant finding, (10) number of patients included, (11) mean age, (12) sex, (13) clinical indications for colonoscopy, (14) relative prevalence of polyps of any size, (15) significant findings, (16) type of bowel preparation adopted, (17) mean level of adequate (excellent or good) bowel preparation at CCE, (18) mean rate of CCE excretion (defined as either capsule excretion or visualization of the hemorrhoidal plexus within the CCE operating time), (19) mean total CCE transit time (from the mouth to the anus), (20) mean colonic CCE transit time, (21) rate of side effects, and (22) type of side effects. Clinically significant findings were defined as polyps 6 mm or larger and/or when more than 3 polyps were present, irrespective of polyp size. We attempted in all cases to identify established cancers separately from polyps. When readings from multiple observers were available, we chose the initial reading by the experimenting center rather than subsequent expert readings that would increase CCE accuracy artificially. An attempt was made to contact the original investigators if data were incomplete or if it was necessary to resolve an apparent conflict or inconsistency in the article.

Risk of Bias in Individual Studies

To assess the methodologic quality of the included studies and detect potential bias, the Quality Assessment of Diagnostic Accuracy in Systematic Reviews was used.[12]

Summary Measures

The primary end point of this systematic review was to address the following questions: (1) what is the per-patient sensitivity and specificity of CCE for polyps of any size? (2) What is the per-patient sensitivity and specificity of CCE for significant findings?

The secondary end point of this systematic review was to address the following questions: (1) What is the per-patient sensitivity of CCE for CRC? (2) What is the rate of capsule excretion? (3) What is the level of excellent-good bowel preparation for CCE? (4) What is the CCE safety profile?

CCE accuracy was defined by a per-patient analysis to emphasize the impact of CCE in a clinical and screening setting rather than the technical ability of CCE to find colonic lesions.

Planned Methods of Analysis

Per-patient sensitivity and specificity values of CCE for polyps of any size and significant findings were summarized by a random-effects model. Heterogeneity was assessed by using the interstudy heterogeneity I^2 statistic.[13] Values of I^2 equal to 25%, 50%, and 75% were assumed to represent low, moderate, and high heterogeneity, respectively. Meta regression analysis

Table 1. Characteristics of the Included Studies

Study	Year of publication	Study country	Full article/ abstract	Centers	Patients, n	Male sex, %	Mean age, y	Patients included, n (%)	Asymptomatic patients, n (%)	Patients with good-excellent bowel preparation, n (%)	Patients with CCE excretion, n (%)[a]
Eliakim et al[5]	2006	Israel	Full article	Multicentric	91	60	57	84 (92)	58 (69)	38 (84)	67 (80)
Schoofs et al[6]	2006	Belgium	Full article	Monocentric	41	37	56	36 (88)	17 (41)	31 (89)	30 (83)
Van Gossum et al[7]	2009	Europe	Full article	Multicentric	332	55	58	320 (96)	0 (0)	230 (72)	302 (94)
Sieg et al[8]	2009	Germany	Full article	Monocentric	38	83	56	36 (95)	36 (100)	28 (88)	27 (75)
Spada et al[15]	2008	Italy	Abstract	Monocentric	40	42	58	40 (100)	18 (45)	17 (42)	35 (88)
Gay et al[16]	2009	France	Full article	Monocentric	128	52	55	126 (98)	74 (58)	103 (82)	114 (90)
Sacher-Huvelin et al[17]	2009	France	Abstract	Multicentric	105	63	60	105 (100)	105 (100)	58 (55)	NA[b]
Pilz et al[18]	2008	Switzerland	Abstract	Monocentric	62	59	59	59 (95)	30 (54)	15 (27)	36 (88)

NA, not applicable.

[a]Refers only to patients included in the analysis.

[b]The authors reported an overall excretion rate of 90%, without distinguishing between those in whom the capsule did not reach the colon and those in whom, after entering into the colon, the capsule was not excreted.

was used to determine the study characteristics that influenced the heterogeneity. This analysis was performed on log-it–transformed proportions by using the meta command of the statistical software. A simple pooling with a 95% confidence interval was obtained for CCE cancer sensitivity because of the expected low number of masses detected in the included studies. The median and range or the mean with 95% confidence intervals (CIs) were used for the descriptive variables, as appropriate.

Risk of Bias Across Studies

A funnel plot was produced for the principal outcomes and the Egger test for funnel plot asymmetry was used to investigate whether publication bias or other small study effects may have affected the results adversely. According to the Egger linear regression for publication bias, a 2-sided *P* value of .10 or less was regarded as significant.[14]

All the calculations were performed with STATA software, including a dedicated integration (StataCorp, Houston, TX; Dwamena BA, 2007 Midas: Stata module for Meta-analytical Integration of Diagnostic Accuracy Studies, University of Michigan Medical School, MI).

Results

Study Selection

A flow diagram of this systematic review is shown in Supplementary Figure 1 (see also Supplementary Table 1 for excluded studies and reasons of exclusion). Eight studies were included in the meta-analysis.[5–8,15–18] The main characteristics of the studies are provided in Table 1. Study design was similar among all the included series, consisting of a prospective technical comparison between CCE and post-CCE colonoscopy, with the endoscopist blinded to CCE results. To obtain further information, 5 investigators were contacted (Supplementary Table 2).

Participants

A total of 837 patients (median age, 57.5 y; range, 54–60 y; median male sex, 57%; range, 37%–83%) were enrolled in the selected studies (Table 1). Overall, 31 (3.7%) patients were excluded from the final analysis of these series (Supplementary Table 3). CCE failure in reaching the colon within the limited operating time (ie, inability to pass the stomach or the small bowel) or to visualize at least 20% of the colonic mucosa were the most frequent exclusion criteria, being reported in 17 (2.3%; 95% CI, 1.2%–3.4%) of 732 cases (1 study did not report this information).

Interventions

All the patients underwent a CCE-dedicated bowel preparation. This regimen consisted of the addition of a sodium phosphate booster to a polyethylene glycol preparation (Supplementary Table 4). The median of the rates of an excellent-good level was 77%, ranging between 27% and 89% among the different series (Table 1). Six studies provided information on the mean colonic transit of the CCE,[5,7,8,15,16,18] whereas 3 series[7,8,18] provided data on the total CCE transit time (from the mouth to the anus). The medians of the CCE colonic and mouth-to-anus transit times were 135 minutes (range, 128–189 min) and 276 minutes (range, 275–291 min), respectively. The exclusion of patients in whom CCE failed to reach the colon within the operating time, as described previously, did not necessarily indicate that in all the included patients the whole colonic mucosa was visualized by the capsule. The CCE excretion rate in the included series was 87% (95% CI, 85%–90%), so that an incomplete CCE colonoscopy occurred in 13% of the cases. When considering cumulatively the CCE failures to either reach the colon (ie, exclusion criteria) or to visualize the whole colonic mucosa once the cecum was reached, the CCE overall excretion rate was estimated to be 86% (95% CI, 83%–88%).

Outcomes

Significant findings were defined as polyps 6 mm or larger in 5 studies[7,8,15,17,18]; and as either polyps 6 mm or larger or 3 or more polyps in 3 studies.[5,6,16]

The prevalence of polyps of any size was specified in 7 studies,[5–8,15,16,18] 1 study reported only that of significant findings,[17] and, similarly, the prevalence of significant findings was reported in 7 studies,[5,7,15,16,17,18] because in one study no case was detected.[8] The overall prevalence of polyps of any size and significant findings at colonoscopy (ie, the reference standard) was 57% (399 cases) and 27.4% (221 cases), respectively (Table 2). Only 21 cancers were described in the included studies, with 19 occurring in one single study.[7]

Risk of Bias Within Studies

Quality assessment of the individual studies is reported in Supplementary Table 5. Patients were recruited consecutively

Table 2. Distribution of Patients With Colorectal Polyps of any Size, Significant Findings, and Cancer in the Selected Studies

Study	N (%)	TP	FP	FN	TN
Patients with Colorectal polyps of any size					
Eliakim et al[5]	36 (43)	20	15	16	33
Schoofs et al[6]	25 (69)	19	4	6	7
Van Gossum et al[7]	212 (66)	153	24	59	84
Sieg et al[8]	11 (31)	6	1	5	24
Spada et al[15]	20 (50)	13	4	7	16
Gay et al[16]	67 (53)	51	14	16	45
Sacher-Huvelin et al[17][a]	NA	NA	NA	NA	NA
Pilz et al[18]	28 (47)	22	14	6	17
Patients with significant findings					
Eliakim et al[5]	16 (19)	8	12	8	56
Schoofs et al[6]	13 (36)	10	7	3	16
Van Gossum et al[7]	87 (27)	56	37	31	196
Sieg et al[8]	0 (0)	0	0	0	0
Spada et al[15]	13 (33)	8	4	5	23
Gay et al[16]	67 (53)	51	14	16	45
Sacher-Huvelin et al[17]	22 (21)	12	11	10	72
Pilz et al[18]	6 (10)	3	13	3	40
Patients with cancer					
Eliakim et al[5]	0	0		0	
Schoofs et al[6]	0	0		0	
Van Gossum et al[7]	19	14		0	
Sieg et al[8]	1	1		0	
Spada et al[15]	1	1		0	
Gay et al[16]	0	0		0	
Sacher-Huvelin et al[17]	0	0		0	
Pilz et al[18]	0	0		0	

NOTE. All the data are calculated based on a per-patient analysis.
TP, true positives; FP, false positives; FN, false negatives; TN, true negatives; NA, not applicable.
[a]In this study only significant findings were reported.

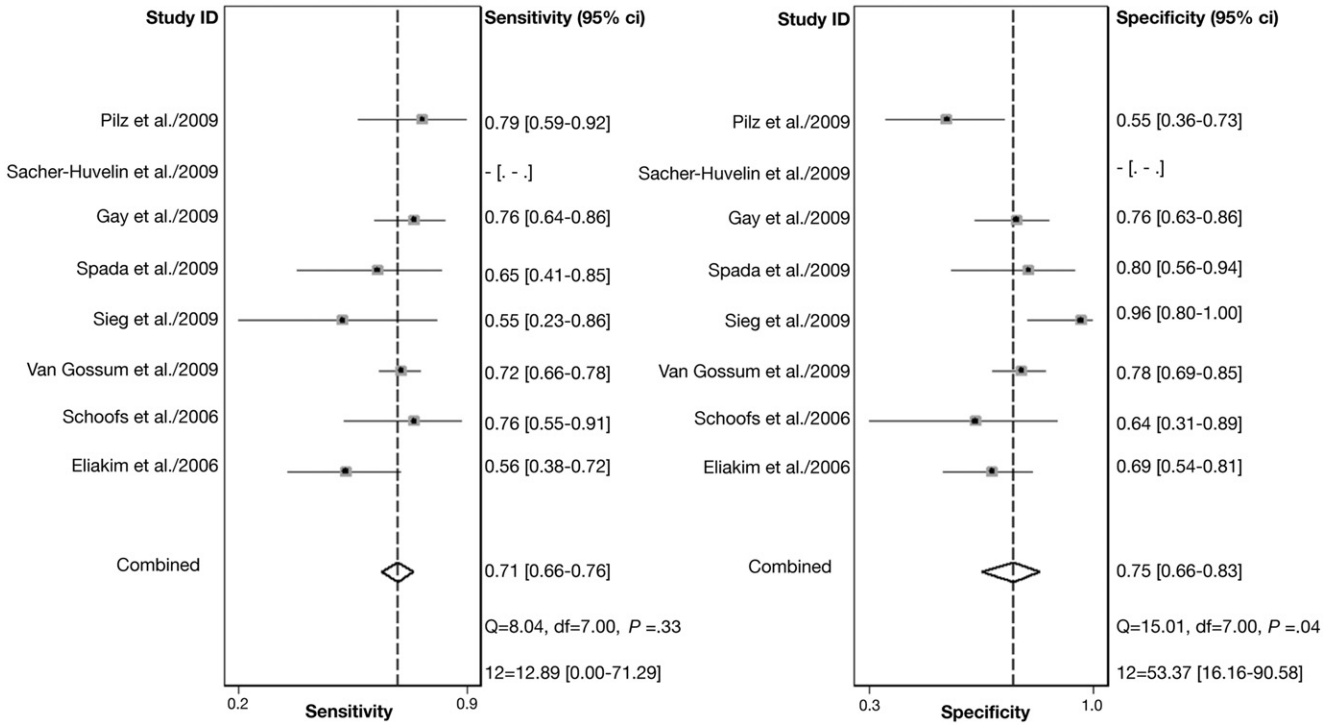

Figure 1. Forest plot of the included studies analyzing the sensitivity and specificity of CCE for polyp of any size.

only in one study,[8] in which 27% of the patients refused to participate, whereas in the other studies a nonconsecutive recruitment prevented a reliable assessment of the withdrawal rate. Only 2 studies enrolled solely asymptomatic subjects,[8,17] whereas an enriched-disease population was included in the remaining studies, so that the study population is unlikely to represent a screening population. Colonoscopy was performed in all the studies immediately after CCE with the endoscopist blinded to CCE results. This was mainly owing to the impossibility of reading CCE examinations before the performance of colonoscopy, with the only exception being one study in which segmental unblinding was performed after cecal intubation.[16] For this reason, eventual false negatives at colonoscopy generally were classified as false positives at CCE, presumably underestimating CCE accuracy. To assess CCE accuracy based on colonoscopy results, a matching-polyp algorithm between CCE and colonoscopy results is required. Such an algorithm was detailed only in one study, in which matching relied purely on polyp size.[7]

Synthesis of Results

Results of individual studies are provided in Table 2.

Polyp of any size. The per-patient summary estimates of sensitivity and specificity for polyps of any size were 71% (95% CI, 66%–76%) and 75% (95% CI, 66%–83%), respectively, as shown in Figure 1. I^2 was 12.9% and 53.4% for sensitivity and specificity, respectively. The moderate degree of heterogeneity when estimating CCE specificity mainly was owing to the only screening study included in this analysis.[8] When excluding this series from the analysis, there was no significant residual heterogeneity (I^2, 26%; $P = .23$), with an estimate of specificity of 72% (95% CI, 65%–78%). Of note, the expected low prevalence of disease in a screening setting may have favored the very high specificity reported from the investigators.[8] Residual heterogeneity was not explained by further analysis at meta-regression.

Significant findings. The per-patient summary estimates of sensitivity and specificity for significant findings were 68% (95% CI, 56%–79%) and 82% (95% CI, 77%–85%), respectively, as shown in Figure 2. I^2 was 61% and 9.2% for sensitivity and specificity, respectively. The moderate degree of heterogeneity when estimating CCE sensitivity was owing to the only series in which unblinding at colonoscopy of CCE results was allowed.[16] When excluding such series, I^2 was equal to 0% with an estimated sensitivity of 62% (95% CI, 54%–69%). Of note, such unblinding may have allowed the reclassification of apparently false-positive CCE results in post-unblinding CCE true-positive results, explaining the higher CCE sensitivity reported by the investigators.[16]

Cancer. Of the 21 carcinomas detected at colonoscopy, 16 were identified by CCE, corresponding to a pooled sensitivity of 76% (95% CI, 58%–94%).

Side effects. Side effects were reported by 7 series.[5–8,15,16,18] Overall, 29 cases occurred in 701 patients, corresponding to a rate of 4.1% (95% CI, 2.6%–5.6%). All the side effects appeared to be mild/moderate (ie, nausea, abdominal pain), with the exception of one case of postpolypectomy peritonitis that was likely to be caused by the operative colonoscopy rather than to CCE examination.

Risk of Bias Across Studies

To explore the low-moderate heterogeneity detected, a funnel plot was drawn. The funnel plot does not show a meaningful asymmetry (Figure 3). The Egger test was not significant ($P = .3$ for a polyp of any size; $P = .8$ for a significant finding).

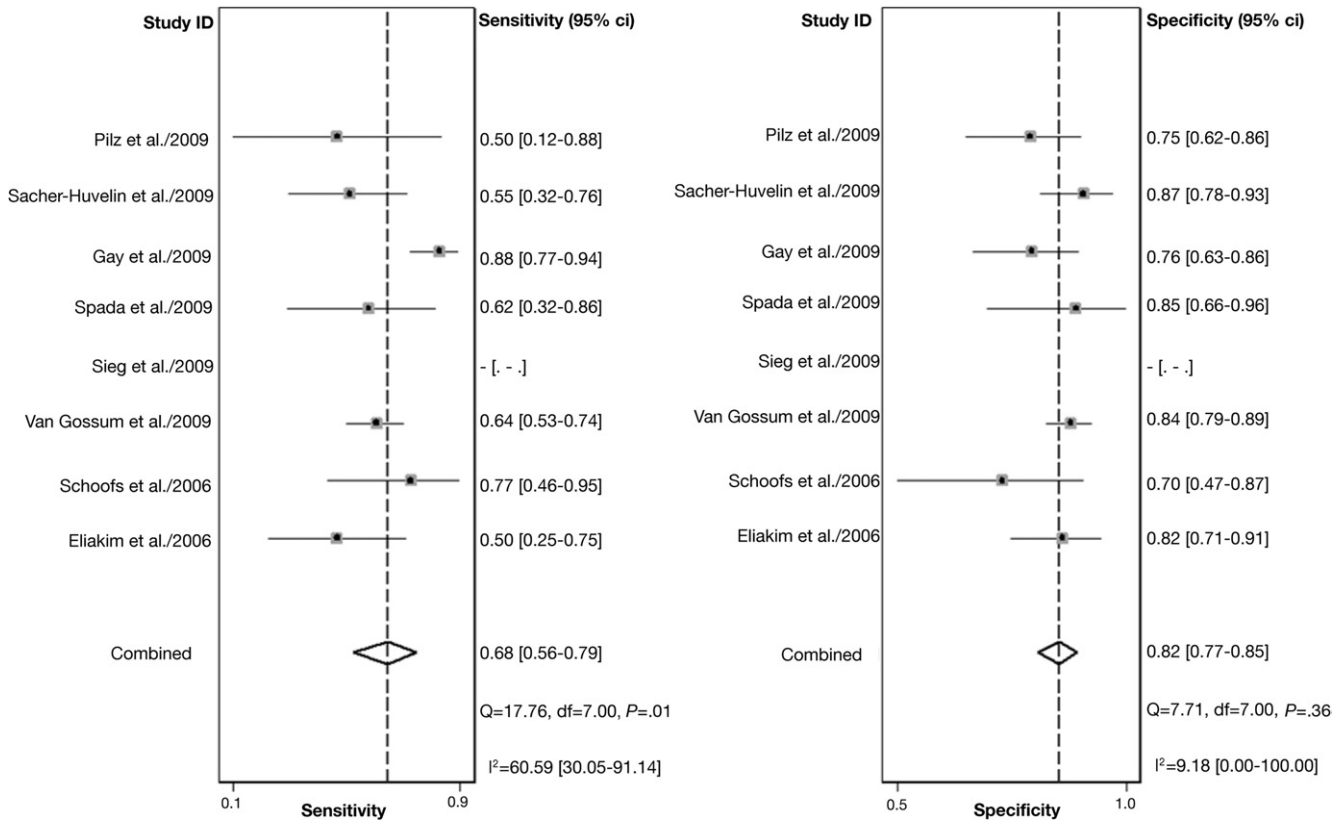

Figure 2. Forest plot of the included studies analyzing the sensitivity and specificity of CCE for significant findings (≥6 mm polyps and/or ≥3 polyps).

Discussion

Our analysis showed that CCE per-patient sensitivity for polyps of any size and significant findings, defined as polyps 6 mm or larger and/or 3 or more lesions, was 71% and 68%, respectively. It could be argued that CCE sensitivity is suboptimal when compared with colonoscopy. However, in a screening setting, population adherence to colonoscopy was disappointingly low, ranging from 10% to 26%,[3,4] so that the apparently higher accuracy of colonoscopy needs to be diluted by such a low compliance.[19] On the other hand, CCE is potentially more attractive than colonoscopy because it is noninvasive, painless, safe, and it is administered by mouth, and not by rectum. Therefore, CCE could compensate its lower accuracy with a higher attendance rate in a screening setting, although this needs to be confirmed by dedicated studies. CCE sensitivity compares favorably with the other noninvasive or less-invasive options for CRC screening. For instance, CCE appears to be substantially more accurate than a fecal test in detecting sig-

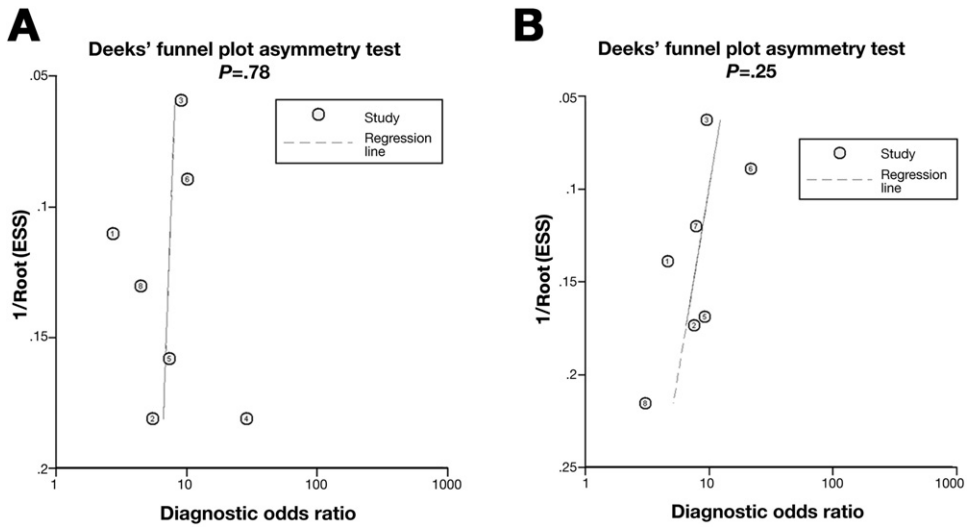

Figure 3. Funnel plot of standard error by odds ratio of all included studies for (*A*) polyp of any size and (*B*) significant findings (≥6 mm polyps and/or ≥3 polyps).

nificant findings; an 11% to 50% sensitivity for advanced neoplasia recently was reported.[20] CCE sensitivity also appears to be similar or superior to that of flexible sigmoidoscopy, which has been reported to identify between 30% and 70% of all colorectal neoplasias.[20] On the other hand, CCE sensitivity appears to be slightly lower than the 78% reported for lesions 6 or more mm for computed tomography (CT) colonography in a recent multicenter trial.[21] Differently from CT colonography, however, CCE is not associated with the risk of radiation-induced cancer,[22] and this may represent an undeniable advantage in a screening setting. However, when taking into account the preliminary stage of this technology, CCE should be reserved for those patients who might be at risk and/or contraindicated for other screening imaging methods, such as colonoscopy.

Of note, only in one study was colonoscopy performed after segmental unblinding because it has been recommended for CT colonography studies.[21] For this reason, our data probably underestimate CCE sensitivity because it is possible that some of the polyps classified as false positive at CCE are indeed false negative at colonoscopy. In particular, a suboptimal sensitivity of colonoscopy, even for large lesions, has been shown in back-to-back studies and in head-to-head comparisons with CT colonography.[23,24] CCE sensitivity for polyps also has been related to the quality of bowel preparation. Our analysis showed that an insufficient cleansing (ie, fair or poor) for CCE was achieved in nearly 30% of the patients. Because of the inability of CCE to suck or wash, this low quality of bowel preparation is likely to have affected the summarized estimate of sensitivity. Of note, a very low rate of good-excellent level of bowel preparation was observed in 3 studies[15,17,18] despite that the preparation regimen was very similar to the remaining series. It is unclear whether this depends on unexplored clinical factors that may affect the quality of preparation at CCE, such as age, sex, or the timing of administration, or on subjective differences in interpreting similar levels of preparation among the studies.

According to our analysis, CCE per-patient specificity was estimated to be 68% and 82% for polyps of any size and significant findings, respectively. Similarly to the sensitivity estimate, CCE specificity may have been underestimated in our analysis because no unblinding of CCE results was performed at colonoscopy in any of the included series except one. For instance, in one study, it was decided that in case of discordance between CCE and colonoscopy, CCE videos were reviewed by an adjudication committee. Specificity before and after adjudication was 87% and 94%, respectively.[17] Another reason to explain this suboptimal CCE specificity may be the training curve of CCE readers. In detail, in one study, 3 different readings of CCE findings were performed according to reader experience. CCE specificity for polyps 6 mm or larger passed from 83% to 100%, when the least and the most expert readers were assessed, respectively.[5]

Only a few cancers were pooled in our study. This is because, on one side, there was a relatively small sample size of included studies, and, on the other side, there was an expected low prevalence of CRC in unselected populations. The 76% CCE sensitivity for cancer, mainly based on the findings of the largest multicenter study included in our series,[7] appears to be suboptimal when compared with both colonoscopy and CT colonography,[21] probably comparable with the sensitivities of the fecal test and flexible sigmoidoscopy.[20] Although at the present time such a suboptimal CCE sensitivity for cancer may argue against the use of CCE in patients at high risk for CRC, such as those 40 years and older with rectal bleeding or anemia, its impact on an eventual application of CCE in a screening setting should be marginalized. Prevalent cancer in 60-year-old asymptomatic subjects is likely to range between 0.2% and 0.4%,[24,25] so that admitting a 76% sensitivity, 1389 asymptomatic subjects should be screened to miss one prevalent cancer. Our study also aimed to assess the quality of the included studies to define the generalizability, the consistency, and the validity of the study results. The strongest aspect of this analysis was that CCE accuracy values were based on an independent reference standard (ie, colonoscopy) that was performed for all the subjects within a very short period of time. The weakest aspect probably was represented by the limited clinical applicability of the study results. In only one study[8] was a consecutive enrolment undertaken, so that the withdrawal rate likely was underestimated because it cannot be excluded that, at least in a screening setting, some patients could refuse either the extensive bowel preparation or the suboptimal accuracy. Moreover, all but 2 studies dealt with a disease-enriched population, so that CCE readers, expecting a high prevalence of polypoid lesions, could have increased their sensitivity artificially at the expense of a lower specificity. Therefore, CCE estimates of accuracy should not be projected immediately in a screening setting. A second weakness was represented by the insufficient description of the polyp-matching algorithm between CCE and colonoscopy in all but one study.[7] This is likely to have overestimated CCE sensitivity because CCE false positives for the index polyp could have been reclassified as true positives because a different polyp was by chance detected by colonoscopy in a different segment of the colon. Moreover, in the only study clearly reporting such methodology, polyp-matching was based purely on size estimates. In particular, reference measurement was performed with biopsy forceps, which is known to be inaccurate, and also CCE size assessment has never been shown to be sufficiently accurate.[7]

A moderate degree of heterogeneity was detected in our analysis, limiting the validity of 2 estimates, namely, specificity for polyps of any size and sensitivity for significant findings. This may warrant the necessity of larger studies in a more controlled setting. However, no high heterogeneity was detected in any of our estimates. When considering the nonrandomized design of the selected studies, this strengthens the meaningfulness of our estimates. A random-effect model also appropriately was chosen to compensate for the moderate heterogeneity detected in these 2 estimates. We also identified the studies responsible for the described heterogeneity, whereas an extensive meta regression analysis and the assessment of publication/small-sample bias failed to depict other confounding factors.

There were limitations to the present analysis. We presented accuracy data for polyps and significant findings with the implicit assumption that post-CCE polypectomy may lead to CRC prevention. However, this hypothesis has been challenged by a recent epidemiologic study showing no CRC incidence or mortality reduction after colonoscopy in the right colon.[26] We included data only for polyps, irrespective of histology. Therefore, we could not assess the accuracy for neoplastic lesions, being likely a loss of specificity because of the CCE identification of hyperplastic polyps. We defined significant findings separately from polyps of any size, with the implicit assumption

that the identification of patients with at least 1 polyp that was 6 mm or larger or 3 or more lesions was the driving force in CRC prevention. However, most of the data on the putative role of these lesions arise from postpolypectomy follow-up studies, in which they simply have been related to a higher risk of advanced neoplasia recurrence.[27] We did not take into account economic implications. A CCE-based screening program has been shown to be substantially more costly than a colonoscopy-based program, when considering the similar cost of the initial procedures coupled with the additional cost for a relevant rate of post-CCE polypectomies and a higher cost for unprevented CRC.[10]

In conclusion, this systematic review provided reliable estimates of CCE accuracy. CCE sensitivity for polyps seems to compare favorably with the other noninvasive options for CRC screening. CCE specificity is likely to be underestimated by the lack of unblinding of CCE results at colonoscopy. These estimates should not be projected immediately in a screening setting because most of the included studies included disease-enriched populations. Future studies should elaborate a more rigorous polyp-matching algorithm between CCE and colonoscopy to avoid incorrect classification of CCE results.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2010.02.018.

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Reprint requests

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Conflicts of interest

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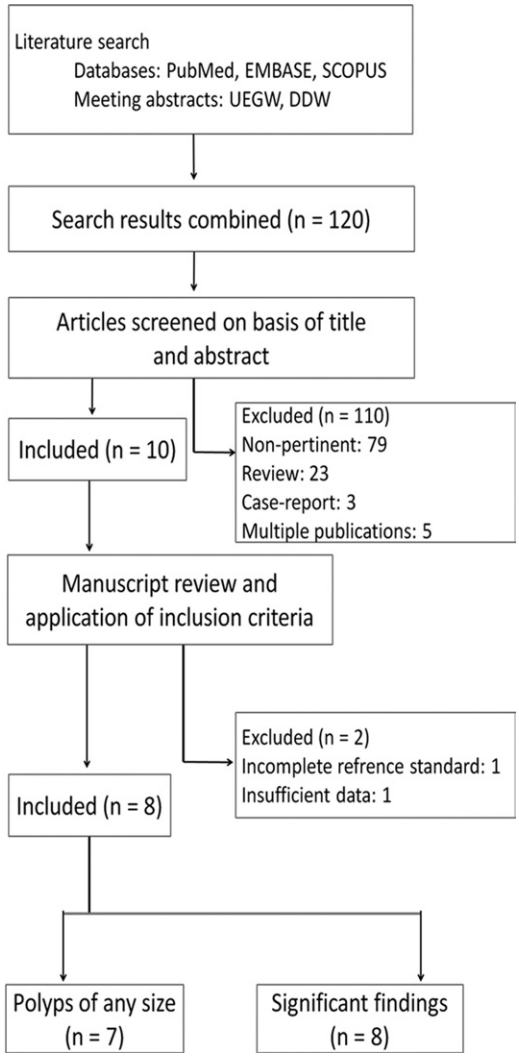

Supplementary Figure 1. Flow-chart of the meta-analysis.

Supplementary Table 1. Reasons for Article Exclusions

Spada C, Riccioni ME, Petruzziello L, et al. The new PillCam colon capsule: difficult colonoscopy? No longer a problem? Gastrointest Endosc 2008;68:807–808. Reason for exclusion: case report.[a]

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[a]Article was excluded after abstract version.
[b]Article was excluded after full paper revision.

Supplementary Table 2. Authors Contacted and Further Information Provided

Pilz (author)[1]: to confirm 2 × 2 extraction; provided further details on bowel preparation, excretion rate of CCE, and mean transit times
Sieg[2]: to confirm 2 × 2 extraction; provided further details on bowel preparation level
Spada (author)[3]: to confirm 2 × 2 extraction; provided further details on bowel preparation, excretion rate of CCE, and mean transit times
Sacher-Huvelin[4]: to confirm 2 × 2 extraction; refused to provide further details on secondary end points because of publication issue
Delvaux/Gay[5]: to confirm 2 × 2 extraction

Supplementary Table 3. Reasons for Exclusion After Initial Enrollment in the Selected Studies

Study	Unable to swallow CCE	CCE in stomach	CCE failure (<20% colon)	Others
Patients excluded, n				
Eliakim et al[6]	1	1	3	2
Schoofs et al[7]	1	—	3	1
Van Gossum et al[8]	1	—	5	6
Sieg et al[2]	—	1	1	1
Spada et al[3]	—	—	—	—
Gay et al[5]	1	—	—	1
Sacher-Huvelin et al[4]	—	—	—	—
Pilz et al[1]	—	1	2	—

Supplementary Table 4. Characteristic of Bowel Preparation

Study	Liters of PEG, n	NaP boosters, n	Prokinetic	Bisacodyl suppository	Low-fiber diet	Clear-liquid diet
Eliakim et al[6]	3	1–2	Tegaserod	Yes	Yes	Yes
Schoofs et al[7]	4	2	Domperidone	Yes	No	Yes
Van Gossum et al[8]	4	2	Domperidone	Yes	No	Yes
Sieg et al[2]	3.5–4	0–2	Domperidone	No	No	Yes
Spada et al[3]	4–5	0–2	Domperidone	Yes	Yes	Yes
Gay et al[5]	4	2	Domperidone	Yes	No	Yes
Sacher-Huvelin et al[4]	NA[a]	NA	NA	NA	NA	NA
Pilz et al[1]	4	2	Domperidone	Yes	Yes	Yes

NOTE. In 3 studies different regimens were applied.[2,3,6]

PEG, polyethylene glycol preparation; NaP, sodium phosphate; NA, not applicable.

[a]The investigators stated that they used PEG, booster, domperidone, and a low-fiber diet, without specifying the doses.

Supplementary Table 5. Quality Assessment of Included Studies Using the 14 Items of the Quality Assessment of Diagnostic Accuracy in Systematic Reviews (QUADAS) Tool

QUADAS item	Eliakim et al[6]	Schoofs et al[7]	Van Gossum et al[8]	Sieg et al[2]	Spada et al[3]	Gay et al[5]	Sacher-Huvelin et al[4]	Pilz et al[1]
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	No	No	No	Yes	No	No	No	No
2. Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Did patients receive the same reference standard regardless of the index test result?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the reference standard independent of the index test (ie, the index test did not form part of the reference standard)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Were uninterpretable/intermediate test results reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Were withdrawals from the study explained?	No	No	No	Yes	No	No	No	No