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Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis

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Abstract
Objectives Previous meta-analyses on CT-colonography included both average and high risk individuals, which may overestimate the diagnostic value in screening. A meta-analysis was performed to obtain the value of CT-colonography for screening.
Methods A search was performed using PubMed, Embase and Cochrane. Article selection and critical appraisal was done by two reviewers. Inclusion criteria: prospective, randomized trials or cohort studies comparing CT-colonography with colonoscopy (≥50 participants), ≥95% average risk participants ≥50 years. Study characteristics and 2×2 contingency Tables were recorded. Sensitivity and specificity estimates were calculated per patient and per polyp (≥6 mm, ≥10 mm), using univariate and bivariate analyses.
Results Five of 1,021 studies identified were included, including 4,086 participants (<1% high risk). I^2-values showed substantial heterogeneity, especially for 6–9 mm polyps and adenomas: 68.1% vs. 78.6% (sensitivity per patient). Estimated sensitivities for patients with polyps or adenomas ≥6 mm were 75.9% and 82.9%, corresponding specificities 94.6% and 91.4%. Estimated sensitivities for patients with polyps or adenomas ≥10 mm were 83.3% and 87.9%, corresponding specificities 98.7% and 97.6%. Estimated sensitivities per polyp for advanced adenomas ≥6 mm and ≥10 mm were 83.9% and 83.8%.
Conclusion Compared to colonoscopy, CT-colonography has a high sensitivity for adenomas ≥10 mm. For (advanced) adenomas ≥6 mm sensitivity is somewhat lower.

Keywords Colorectal cancer · Screening · CT-Colonography · Colonoscopy · Sensitivity and specificity

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Introduction

Computed tomography (CT)-colonography has been studied for screening for (precursors of) colorectal cancer (CRC) and the Multisociety Task Force on Colorectal Cancer has indicated CT-colonography as an acceptable technique for CRC screening [1, 2]. However, recently the National Institute of Health has published a statement regarding CRC screening concluding that there is still lack of information regarding the use of CT-colonography as screening technique in an average risk population [3]. Also other guidelines state that there is insufficient evidence yet [4, 5].

Several meta-analyses have been published on the diagnostic value of CT-colonography including both average risk and high risk individuals, but no meta-analysis has been published including average risk individuals only [6–10]. Individuals are considered to be at average risk if they have no symptoms, no personal history of CRC,

adenomatous polyps or inflammatory bowel disease and no family history of advanced neoplasia [11]. By including studies containing high risk populations, the diagnostic value of CT-colonography in an average risk population might be overestimated. It is known that the estimated diagnostic value of a technique depends on factors such as disease prevalence and spectrum.

Therefore, the aim of this meta-analysis was to estimate the diagnostic value of CT-colonography to detect (advanced) adenomas and CRC in an average risk population aged 50–75 years.

Materials and methods

Literature search

Articles were obtained from the electronic databases PubMed, Embase and Cochrane, without restrictions with respect to the publication date and language. Lists of synonyms for CT-colonography were produced (Fig. 1) and combined using the Boolean operator "OR". The same was done for colonoscopy. Both search results were combined, using the Boolean operator "AND". By reading title and abstract of all retrieved articles, two observers identified possible relevant papers, based on the inclusion and exclusion criteria described below. The remaining articles were retrieved as full-text articles and independently checked by two reviewers. Disagreement regarding inclusion was resolved by consensus. Reference lists of the final selection of articles were checked manually to identify other relevant papers. If additional information of an article considered for inclusion was needed due to incomplete data or description of the methods, the corresponding authors were contacted.

Inclusion and exclusion criteria

Inclusion criteria were prospective, randomized trials or cohort studies, in humans ≥50 years, in which at least 50 predominantly asymptomatic average risk subjects (≥95%) underwent CT-colonography and completed colonoscopy for verification within 3 months. In addition, eligible studies needed to report the detection of colorectal polyps (adenomatous and non-adenomatous), advanced neoplasia and CRC and should include true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) values. Studies that included predominantly high risk subjects (symptomatic, history of hereditary CRC, personal history of polyps, CRC or IBD) were excluded, as well as studies that performed CT-colonography as a consequence of incomplete colonoscopy or studies that only performed colonoscopy after positive findings on CT-colonography.

Quality assessment

Systematic assessment of quality and documentation of relevant data of the selected articles was performed independently by two reviewers, using a standardized form. To grade the study quality, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used with special focus on the characteristics of the included study population, index test and reference test [12]. We assessed whether the inclusion and exclusion criteria were described clearly and would result in a representative screening cohort. In addition,the presence of a disease progression bias and a verification bias was determined: did *all* participants receive their reference test <3 months? Furthermore, we assessed whether the index test did not form part of the reference standard, whether all subjects received the same reference test, if the test results of both test were interpreted without knowledge of the other test results and whether withdrawals or uninterpretable test results were reported. Results are presented in Appendix 1.

Study population

The following patient characteristics were documented: number of asymptomatic and symptomatic subjects, sex ratio, mean or median age with age range and CT-colonography indication.

Imaging features

The following characteristics were documented regarding the imaging features of CT-colonography: bowel preparation, dietary restrictions, tagging and bowel distention, use of spasmolytical drugs and type of CT-system and CT-parameters, the positioning of the patient and the use of intravenous contrast medium during CT-colonography. For colonoscopy, the type of bowel preparation and dietary restrictions were documented.

Imaging and diagnostic criteria

The following characteristics were documented regarding image analysis of both CT-colonography and colonoscopy: number of diagnostic examinations, number and experience of CT-colonography readers and endoscopists, reading strategy on CT-colonography, use of segmental unblinding or second look colonoscopy, determination of size on CT-colonography and during colonoscopy and histopathological confirmation.

Data extraction

For the analysis per patient, 2×2 contingency tables were constructed to be able to calculate the sensitivity and

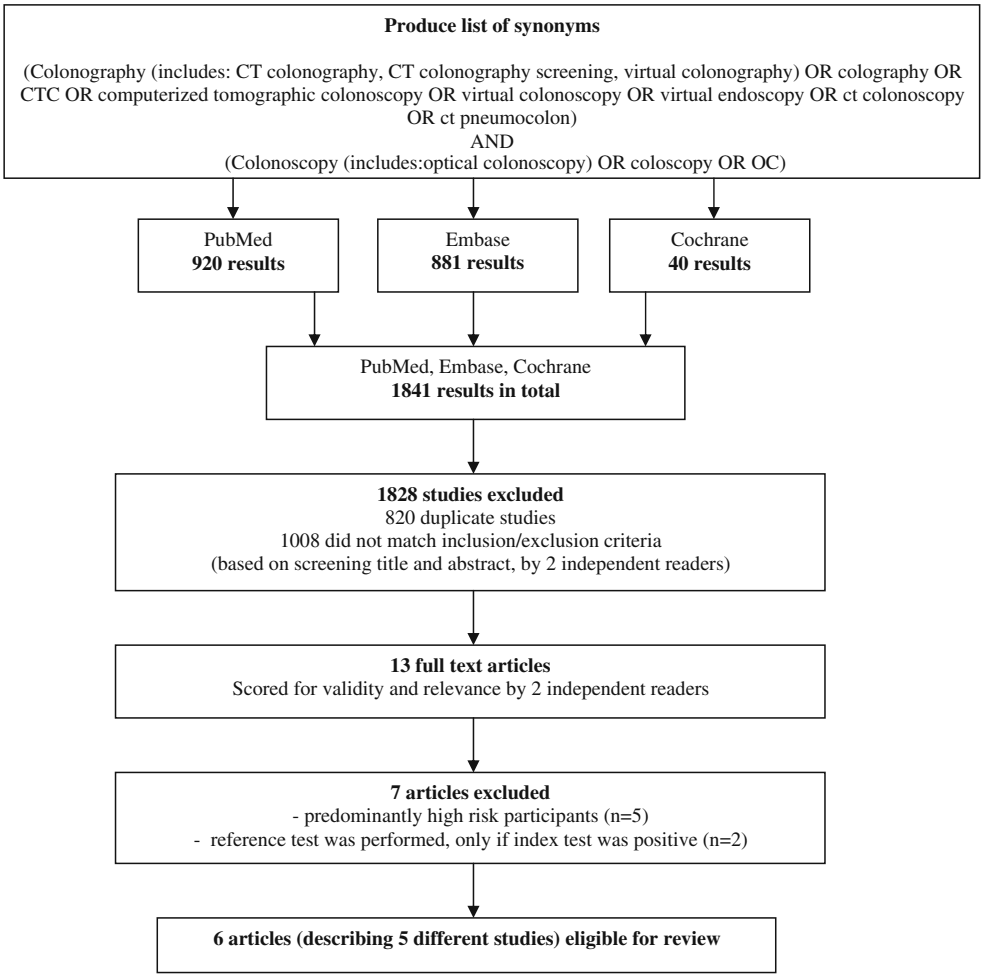

Fig. 1 Flowchart of search strategy, search date: 21st of July, 2010

specificity values for the following type of lesions: all polyps, adenomatous polyps, advanced adenomas (defined as an adenoma with >25% villous features, size ≥10 mm and/or high grade dysplasia [13]), advanced neoplasia and CRC. For each type of lesion, except for CRC, data were collected using the following thresholds: 6–9 mm, ≥6 mm and ≥10 mm, based on the associated potential CRC risk [14–16].

For the analysis per polyp, we extracted TP and FN findings to calculate the sensitivity of all polyps, (advanced) adenomas and advanced neoplasia for the same thresholds.

If needed, a request for additional data was send to the corresponding author. If possible, the following matching algorithm was used: the lesion should be at least <50% margin of error in size and should be found in the same or adjacent segment.

Statistical analysis

Heterogeneity of sensitivity or specificity was assessed using I^2 statistics [17]. If I^2 values were >25%, we considered these data significantly heterogeneous, and random-effects analyses were performed. In case of I^2-values <25%, fixed-effects approaches were used.

For the per-patient analyses, we used bivariate models [18] to obtain summary estimates of sensitivity and specificity with 95% confidence intervals. For the per-polyp analyses, we used univariate models to obtain summary estimates of sensitivity with 95% confidence intervals. All analyses were performed using SAS software (SAS 9.2 procNlmixed, SAS Institute, Cary, NC, USA).

Publication bias was examined by constructing funnel plots.

Per patient The x-axis consisted of the natural logarithm of the diagnostic odds ratio $(= (\mathrm{TP} \times \mathrm{TN})/(\mathrm{FN} \times \mathrm{FP}))$. On the y-axis, we plotted the number of patients.

Per-lesion The x-axis consisted of the sensitivity and on the y-axis, we plotted the number of patients.

Egger's regression tests were used to examine the asymmetry of the funnel plots. A significant regression coefficient ($P<0.05$) indicates an association between sample size and the diagnostic values.

Results

The initial search yielded 1,841 articles (Fig. 1). By excluding doubles, 1,021 articles remained. After screening on title and abstract, 1,008 articles were excluded. The most frequent reasons for exclusion were study design, study population (i.e. high risk) or non-related to CT-colonography or screening for polyps and CRC (i.e. IBD, MR-colonography). After assessment of 13 full text publications, seven articles were excluded, because they included only (n=2)[19, 20] or predominantly (n=4) high risk participants (16.7%, 37.0%, 76.6% and 80.4%, respectively)[21–24] or because colonoscopy was only offered to a small selection of the participants (n=1) [25]. Finally, six articles were included in this systematic review describing the results found in five prospective cohort studies [26–31]. Screening of title and abstract of references and related articles did not result in additional relevant articles.

Patient characteristics

Patient characteristics are outlined in Table 1. We included five studies with in total 4,086 patients (54% male). Four studies [26–28, 30, 31] did have a study population of over 200 average risk subjects, the largest population comprised 2,249 average risk subjects [27]. The smallest study had a population of 68 participants at average risk [29]. All studies provided a clear description of patient characteristics and the inclusion and exclusion criteria. Three studies included high risk subjects: 2.6% [30, 31], 5.2% [28] and 11.3% [27], respectively. The corresponding authors of these papers were contacted to obtain data concerning average risk patients only. This succeeded in two out of three studies, resulting in a total of four datasets containing data of average risk subjects only [26–29] and one study including 2.6% high risk participants [30, 31]. Resulting in a total of 4,086 participants, of which 37 were at high risk (0.9%). The mean age varied between 55 and 60.5 years, the minimal age was 50 in four studies [26–29].

Bowel preparation and CT-colonography procedure

Bowel preparation and CT-colonography procedure are outlined in Appendix 2.

Three studies used an extensive bowel preparation predominantly based on 4 liters polyethylene glycol [26–28] combined with a clear liquid diet [26], a low-residue diet [28] or dietary restrictions depending on the institutional standard of the clinical centres where the examinations were done [27]. The remaining two studies both used a more limited preparation based on sodium phosphate [29–31]. One study combined this with a clear liquid diet [30, 31], the dietary restrictions of the other study were not specified [29].

Three studies used oral tagging [26, 27, 30, 31], one study did use intravenous contrast medium [28]. Of one study it was not specified whether the participants received tagging [29]. Bowel preparation was the same for colonoscopy, as both colonoscopy and CT-colonography were performed on the same day in all studies.

Bowel distension methods varied between the studies. Two studies used (primarily) automated CO_2 insufflation, combined with butylscopolamine bromide (Buscopan, Boehringer, Ingelheim, Germany) [26] or glucagonhydrochloride (GlucaGen, Novo Nordisk A'S, Bagsvaerd, Denmark) as spasmolytical drug [27]. Three studies used manual room air [28–31]. In one study no spasmolytical drug was administered [28], it was not specified whether spasmolytical drugs were used in the remaining two studies [29–31]. Two studies used at least 4 slice CT equipment [29–31], two studies used at least 16 slice CT [27, 28] and one study used 64 slice CT [26].

Study characteristics

Study characteristics are outlined in Appendix 3. All participants received CT-colonography and colonoscopy on the same day. Different reference standards were used. One study used the colonoscopy results without knowledge of the CT-colonography findings [29], two studies used the colonoscopy result after segmental unblinding as reference [26, 30, 31], one study used colonoscopy (followed by a second look colonoscopy if lesions ≥10 mm reported on CTC were missed on the initial colonoscopy) combined with histopathology as reference [27] and another study used the histopathology results of the polyps that were removed during colonoscopy after segmental unblinding [28]. It is unclear whether there were any withdrawals in the selected studies. Uninterpretable results of CT-colonography or colonoscopy (outlined in Table 1) were reported and excluded from the analyses in two studies [26, 30, 31].

Image analysis

The characteristics of the readers and the reading strategy are outlined in Appendix 3. The minimal experience of the CT-colonography readers was specified in four out of five studies, and varied between 25 and 100 examinations [26–28, 30, 31]. In one study the only reader had 5 years of reading experience [29]. Two studies used 2D read as primary reading strategy [28, 29], two studies used 3D read [26, 30, 31] and one study used both reading strategies at random [27]. None of the included studies specified whether CAD was used. The experience of the endoscopists and use of different scopes of the included studies was not specified in most studies [27, 29–31]. One study had been done by gastroenterologists with a minimum experience of 1,000

Table 1 Patient characteristics included studies

Author	Multicenter or single center trial (n) and design	Inclusion criteria	Exclusion criteria	Number of subjects, included in analysis	M:F	Age (mean, median, range)
Graser 2009 [26]	Single, prospective	≥50 year asymptomatic[a]	prior OC previous 5 years; positive family history for CRC or hereditary CRC syndromes; history of IBD; body weight >150 kg; severe cardiovascular or pulmonary disease	311 participants 4 excluded: 2 no colonoscopy and 2 incomplete colonoscopy Included in analysis: 307	171:140	60.5 59.7 50–81
Johnson, 2008 [27]	Multi (*n*=15), prospective	≥50 year asymptomatic[b]	prior OC previous 5 years; positive family history for CRC or familial polyposis syndrome; personal history of IBD, polyps and/or CRC; positive FOBT; serious medical condition that increases complication risk colonoscopy	2,249	1088:1161	58.0 57.0 50–86
Kim, 2008 [28]	Single, prospective	≥50 year asymptomatic[c]	prior OC previous 5 years; positive family history for CRC or hereditary CRC syndromes (FAP or HNPCC); history of IBD, adenomatous polyps, bowel obstruction, ischemic colitis or colorectal surgery; positive FOBT previous 6 months; medical condition that preclude the use of bowel preparation or colonoscopy	229	159:70	58.1 n.a. 50–76
Macari, 2004 [29]	Single, prospective	≥50 year asymptomatic (not specified)	prior sigmoidoscopy, DBCE examination or colonoscopy; positive family history for CRC, history of polyps; positive FOBT;	68	68 men	55 n.a. 50–67
Pickhardt, 2003 [30, 31]	Multi (*n*=4), prospective	50–79 year asymptomatic[d] average risk 40–79 year asymptomatic[d] positive family history of CRC	prior OC previous 10 years or prior barium enema previous 5 years; positive family history for hereditary CRC syndromes (FAP or HNPCC); history of IBD, adenomatous polyps or CRC; positive guaiac-based stool test previous 6 months; medical condition that precludes the use of sodium phosphate preparation; pregnancy	1,253 participants 20 excluded: 6 inadequate preparation, 8 incomplete colonoscopy, 6 incomplete CTC Included in analysis: 1.233 (3% high risk)	728:505	57.8 56 40–79

[a] asymptomatic=free of symptoms of colonic diseases such as melena, haematochezia, diarrhoea, relevant changes in stool frequency or abdominal pain

[b] asymptomatic=no melena, anemia or hematochezia more than ones last 6 months, no lower abdominal pain

[c] asymptomatic=no significant GI signs or melena, hematochezia, iron-deficiency anemia, weight loss or abdominal pain within 6 months before study

[d] asymptomatic=no iron deficiency anemia last 6 months, no melena or hematochezia last 12 months, no unintentional weight loss >10 lb (4.5 kg) last 12 months

colonoscopies [26], while the gastroenterologists in another study had a prior experience of 3,000 colonoscopies [28].

Size measurement of the polyp was done by the use of an open biopsy forceps [26, 28, 29], by a calibrated linear probe [30, 31] or determined by the pathologist [27]. In all studies histopathology confirmation was available.

Data extraction

Four studies used a matching algorithm almost the same as the one described in the methods [26, 28–31]. These studies considered a CT-colonography finding to correspond with a colonoscopy lesion, if it was found in the same or adjacent segment. In addition it should be at least <50% margin of error in size [28], in the same or adjacent size category [26, 30, 31] or should have a size difference of <4 mm [29] to be considered as a true positive. The fifth study [27] used a different matching algorithm: one or more lesions should be in the same size category, irrespective of location. Of this study new data were requested and received, using the matching algorithm as specified in the methods section.

Per patient data for each of the different size categories regarding all polyps and adenomas respectively, could be obtained in three respectively four of the five studies (Table 2). Per polyp data for each of the different size categories regarding all polyps could be obtained in all studies while per polyp data for adenomas could be obtained in four studies and per polyp data of advanced adenomas and CRC in three of the five studies (Table 3).

Corresponding I^2 values for heterogeneity are reported in Tables 2 and 3. The results of individual studies are shown in forest plots (Figs. 2 and 3).

Table 2 Results regarding all polyps, (advanced) adenomatous polyps, colorectal cancer, advanced neoplasia: per patient

		All polyps (n=2,853)											
		6–9 mm				≥6 mm				≥10 mm			
		TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN
Graser [26]	N=307	25	6	4	272	50	10	6	241	25	4	2	276
Johnson [27]	N=2,249	78	58	51	2,062	156	75	70	1,948	78	17	19	2,135
Kim [28]	N=229	23	14	15	177	36	20	17	156	13	6	2	208
Macari [29]	N=68	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	3	1	0	64
Estimated sensitivity		68.1 (52.9–80.2)				75.9 (62.3–85.8)				83.3 (76.8–89.0)			
I^2 heterogeneity[a]		68.2% (29.2–85.7)				77.0% (46.0–90.2)				0.0% (0.0–82.0)			
Estimated specificity		96.5 (93.9–98.0)				94.6 (90.4–97.0)				98.7 (97.6–99.3)			
I^2 heterogeneity[a]		83.7% (61.7–93.1)				90.4% (78.5–95.7)				60.1% (15.2–81.2)			
		Adenomatous polyps (n=4,018)											
		6–9 mm				≥6 mm				≥10 mm			
		TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN
Graser [26]	N=307	19	12	2	274	42	18	4	243	23	6	2	276
Johnson [27]	N=2,249	62	61	30	2,096	137	78	45	1,989	75	17	15	2,142
Kim [28]	N=229	22	6	11	190	31	18	12	168	9	12	1	207
Pickhardt [30, 31]	N=1,233	104	170	16	943	149	217	19	848	45	47	3	1,138
Estimated sensitivity		78.6 (66.1–87.3)				82.9 (73.6–89.4)				87.9 (82.1–92.0)			
I^2 heterogeneity[a]		79.4% (54.2–90.8)				80.2% (56.0–91.1)				14.6% (0.0–87.0)			
Estimated specificity		95.0 (89.7–97.6)				91.4 (84.1–95.5)				97.6 (95.0–98.9)			
I^2 heterogeneity[a]		98.1% (96.9–98.8)				98.4% (97.6–99.0)				92.5% (85.3–96.2)			
		Advanced adenomas ≥6 mm, advanced neoplasia ≥6 mm and CRC (n=2,785)											
		Advanced adenomas ≥6 mm[c] sensitivity				Colorectal cancer[c] sensitivity				Advanced neoplasia ≥6 mm[c] sensitivity			
Graser [26]	N=307	92.6%				100%				92.9%			
Johnson [27]	N=2,249	83.3%				100%				84.0%			
Kim [28]	N=229	87.5%[b]				100%				88.2%[b]			

[a] If I^2 values of sensitivity and/or specificity were larger than 25%, data were considered as significantly heterogeneous

[b] No lesions <6 mm found

[c] Not possible to calculate estimated sensitivity and specificity due to small numbers, data regarding TP, FP, FN and TN values not available

Table 3 Results regarding all polyps, (advanced) adenomatous polyps, colorectal cancer and advanced neoplasia: per polyp

		All polyps (n=4,086 participants)					
		6–9 mm		≥6 mm		≥10 mm	
		TP	FN	TP	FN	TP	FN
Graser [26]	N=307	49	7	84	9	35	2
Johnson [27]	N=2,249	113	74	203	97	90	23
Kim [28]	N=229	44	34	60	40	16	6
Macari [29]	N=68	9	8	12	8	3	0
Pickhardt [30, 31]	N=1,233	209	54	278	66	69	12
Estimated sensitivity		69.7 (56.2–80.6)		74.3 (61.6–83.8)		83.7 (76.6–89.0)	
I^2 heterogeneity[a]		88.6% (77.8–94.2)		89.3% (79.3–94.4)		33.3% (0.0–56.9)	
		Adenomatous polyps (n=4,018 participants)					
		6–9 mm		≥6 mm		≥10 mm	
		TP	FN	TP	FN	TP	FN
Graser [26]	N=307	37	4	67	6	30	2
Johnson [27]	N=2,249	81	49	167	68	86	19
Kim [28]	N=229	31	21	44	25	13	4
Pickhardt [30, 31]	N=1,233	133	26	180	30	47	4
Estimated sensitivity		75.7 (60.3–86.5)		80.0 (66.9–88.7)		85.9 (80.4–90.0)	
I^2 heterogeneity[a]		88.5% (75.9–94.5)		89.2 (77.7–94.8)		44.9% (2.8–68.8)	
		Advanced adenomas (n=2,785 participants)					
		6–9 mm		≥6 mm		≥10 mm	
		TP	FN	TP	FN	TP	FN
Graser [26]	N=307	6	0	36	2	30	2
Johnson [27]	N=2,249	0	0	86	19	86	19
Kim [28]	N=229	6	2	19	6	13	4
Estimated sensitivity		n.a.		83.9 (77.6–88.7)		83.8 (77.1–88.8)	
I^2 heterogeneity[a]		n.a.		51.8 (16.2–72.3)		32.3% (0.0–93.0)	
		Colorectal cancer (n=2,785 participants)					
		6–9 mm		≥6 mm		≥10 mm	
		TP	FN	TP	FN	TP	FN
Graser [26]	N=307	0	0	1	0	1	0
Johnson [27]	N=2,249	0	0	4	0	4	0
Kim [28]	N=229	0	0	1	0	1	0
Not possible to calculate estimated sensitivity due to small numbers							
		Advanced neoplasia (n=2,785 participants)					
		6–9 mm		≥6 mm		≥10 mm	
		TP	FN	TP	FN	TP	FN
Graser [26]	N=307	6	0	37	2	31	2
Johnson [27]	N=2,249	0	0	90	19	90	19
Kim [28]	N=229	6	2	20	6	14	4
Not possible to calculate estimated sensitivity due to small numbers							

[a] If I^2 values of sensitivity and/or specificity were larger than 25%, data were considered as significantly heterogeneous

Data analysis per patient

All polyps Estimated sensitivities for polyps ≥6 mm and ≥ 10 mm (regardless of histology) were 75.9% (95%CI 62.3–85.8) and 83.3% (95%CI 76.8–89.0), while corresponding specificities were 94.6% (95%CI 90.4–97.0) and 98.7% (95%CI 97.6–99.3).

Adenomas Estimated sensitivities for adenomas ≥6 mm and ≥10 mm were 82.9% (95%CI 73.6–89.4) and

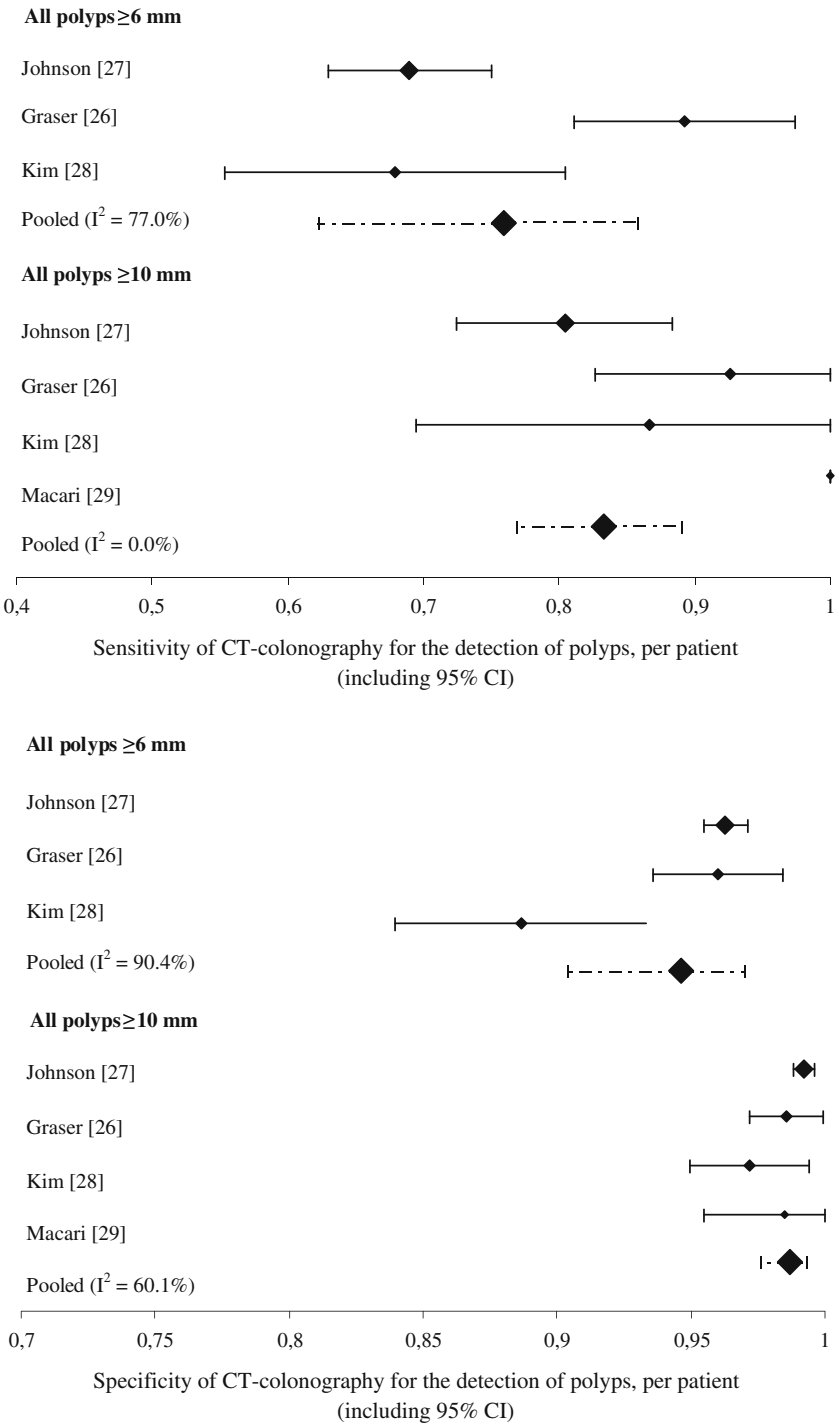

Fig. 2 Forest plot of per patient sensitivity and specificity, including sensitivity and specificity estimates, for all polyps. Summary statistics: estimated sensitivities for polyps ≥6 mm and ≥10 mm were 75.9% (95% CI 62.3–85.8) and 83.3% (95% CI 76.8–89.0), corresponding estimated specificities 94.6% (90.4–97.0) and 98.7% (97.6–99.3)

87.9% (95%CI 82.1–92.0), while corresponding specificities were 91.4% (95%CI 84.1–95.5) and 97.6% (95%CI 95.0–98.9).Estimated sensitivities of all polyps and adenomatous polyps of 6–9 mm are available in Table 2.

Advanced adenomas, CRC and advanced neoplasia Estimated results for the detection of advanced adenomas, advanced neoplasia and CRC were not calculated, as a consequence of the small number of participants with these findings (Table 2).

Data analysis per polyp

All polyps Estimated sensitivities for polyps ≥6 mm and ≥10 mm (regardless of histology), were 74.3% (95%CI 61.6–83.3) and 83.7% (95%CI 76.6–89.0).

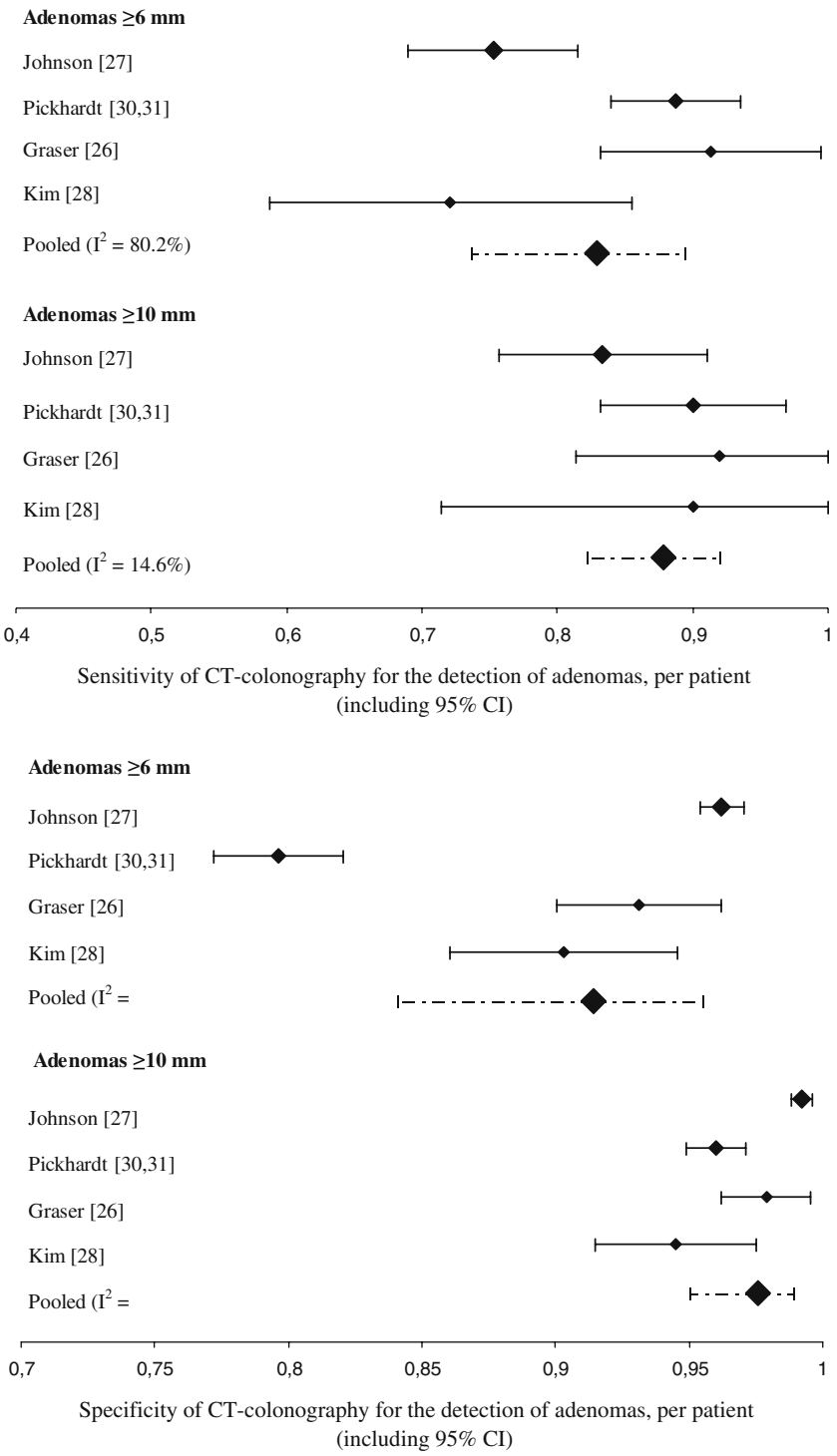

Fig. 3 Forest plot of per patient sensitivity and specificity, including sensitivity and specificity estimates, for adenomas Summary statistics: estimated sensitivities for adenomas ≥6 mm and ≥10 mm were 82.9 (73.6–89.4) and 87.9 (82.1–92.0), corresponding estimated specificities 91.4 (84.1–95.5) and 97.6 (95.0–98.9)

Adenomas Estimated sensitivities for adenomas ≥6 mm and ≥10 mm were 80.0% (95%CI 66.9–88.7) and 85.9% (95%CI 80.4–90.0).

Advanced adenomas Estimated sensitivities for advanced adenomas ≥6 mm and ≥10 mm were 83.9% (95%CI 77.6–88.7) and 83.3% (95%CI 77.1–88.8). Estimated sensitivities for polyps and (advanced) adenomas of 6–9 mm, are presented in Table 3.

Advanced neoplasia and CRC Estimated sensitivities for advanced neoplasia and CRC by CT-colonography were not calculated, as a consequence of the small number of CRCs (n=6) that were detected in the

included studies. In all studies, no CRCs were missed (Table 3).

Publication bias

The data points in the funnel plots are symmetrically distributed in a funnel shape suggesting the absence of publication bias (Appendix 4a–5b). In addition, the Egger's regression tests showed no associations between sample size and diagnostic values (data not shown).

Discussion

This systematic review demonstrates an estimated per patient sensitivity and specificity of CT-colonography for the detection of adenomas ≥6 mm of 82.9% (95%CI 74–89%) and 91.4% (95%CI 84–96%) in asymptomatic screening participants. The estimated per patient sensitivity and specificity for adenomas ≥10 mm, were 87.9% (95%CI 82–92%) and 97.6% (95%CI 95–99%). The estimated per patient sensitivities for all colorectal polyps were slightly lower. All six CRCs were detected by CT-colonography.

As we obtained additional data of the studies in which high risk participants were excluded [27, 28], the study results might not be identical to previously published data. In addition, the results of Johnson et al. [27] are different then published before, as we used a different matching algorithm then the one that was used in their study, resulting in lower sensitivities and higher specificities.

There are a few explanations available for the substantial variability between studies in sensitivity and specificity. The largest study [27] (n=2,249 participants), did not report lesions <5 mm found on CT-colonography (while a colonoscopy lesion of 6 mm could match a CTC lesion of 3 mm) and performed no second look colonoscopy for colonoscopy negative CTC lesions <10 mm . Obviously, both factors will probably result in a lower sensitivity for medium sized adenomas and a less prominent difference in the detection of adenomas ≥10 mm compared to the studies of Graser [26] and Pickhardt [30, 31]. The second explanation could be the use of primary 2D or primary 3D read: those studies with the highest sensitivities for the detection of adenomas used primary 3D read [26, 30, 31]; the other studies used primary 2D read [28, 29] or both methods randomly [27]. However, there is conflicting evidence regarding the possible difference of sensitivity when using primary 2D or 3D read [32, 33].

To our knowledge this is the first meta-analysis in which the diagnostic value of CT-colonography is compared to colonoscopy for the detection of (adenomatous) polyps and CRC in an average risk population. Previously, at least five systematic reviews [6–10] were published describing the diagnostic value of CT-colonography in general (not specified for (advanced) adenomas), including both average risk and high risk populations. By comparing our results to the estimated sensitivities per patient for polyps 6–9 mm and ≥10 mm published previously, we found lower sensitivities, especially when looking at polyps of 6–9 mm. Estimated sensitivities per patient for polyps 6–9 mm published before were 59%, 70%, 84% and 86%, respectively [6–8, 10], while we calculated an estimated sensitivity of 68.1%. Estimated sensitivities per patient for polyps ≥10 mm were 76%, 85%, 88% and 93%, respectively [6–8, 10], while we calculated an estimated sensitivity of 83.3%. The fifth meta-analysis reported results using different thresholds [9].

Our study has several strengths. We aimed to use data on average risk participants only and collected data regarding all polyps, (advanced) adenomas and CRC. This provided the possibility to estimate the diagnostic value of CT-colonography for adenomas and CRC in a screening setting. In order to perform an unbiased study selection, two reviewers independently selected possible relevant articles.

Our study also has several limitations. Although we tried to include only individuals at average risk, we could not obtain these data from one study [30, 31]. Therefore, 37 individuals (0.9%) at high risk were included. However, it is assumable that this will be daily practice in screening and it is unlikely that this small number will have a substantial impact on the results.

Secondly, participants of two studies comprised the majority of included participants, which might give the impression that this meta-analysis is actually a two study meta-analysis. However, the results of the two largest studies were heterogeneous and, moreover, were not at one end of the spectrum of the sensitivity or specificity range. Therefore it is unlikely that the larger studies skewed the results in one direction (of higher or lower values). Furthermore, sensitivity and specificity estimates were calculated using statistical analyses in which the individual studies are weighted by number of included participants [18].

Thirdly, we did not calculate the negative predictive value (NPV) because the prior probability of a negative outcome was high [34].

Fourthly, it is known that colonoscopy is not 100% sensitive for colorectal lesions and therefore no perfect reference standard [35]. Using the colonoscopy results after segmental unblinding and compared with histology, would be the best reference standard.

Fifthly, because of limited data we were not able to calculate estimated sensitivities per patient for the detection of advanced adenomas, advanced neoplasia and CRC.

In summary, this meta-analysis of prospective studies studying the diagnostic value of CT-colonography compared to colonoscopy in an average risk population, shows that CT-colonography has a good sensitivity for (advanced) adenomas ≥10 mm. For (advanced) adenomas ≥6 mm sensitivity is somewhat lower.

Acknowledgment The authors acknowledge the authors of the included studies [26, 28–31] and the American College of Radiology Imaging Network [27] for providing us with additional data.

Appendix 1

Table 4 Quality assessment of all included studies using the QUADAS-tool

	Graser, 2009 [26]	Johnson, 2008 [27]	Kim, 2008 [28]	Macari, 2004 [29]	Pickhardt, 2003 [30, 31]
Spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes	Yes	Yes
Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes
Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes
Is the time period between reference standard and index test short enough to prevent change of the target condition between the two tests?[1]	Yes, same day	Yes, same day	Yes, same day	Yes, same day	Yes, same day
Did all subjects receive verification using a reference standard of diagnosis?	Yes	Yes	Yes	Yes	Yes
Did all subjects receive the same reference standard regardless of the index test result?	Yes	Yes	Yes	Yes	Yes
Was the reference standard independent of the index test?	No[2]	No, partly[3]	No[2]	Yes	No[2]
Execution of the index test described in sufficient detail to permit replication?	Yes	Yes	Yes	Yes	Yes
Execution of the reference standard described in sufficient detail to permit replication?	Yes	Yes	Yes	Yes	Yes
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Yes	Yes	Yes	Yes
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
Were uninterpretable/intermediate test results reported?	Yes	Yes, partly[4]	Unclear	Unclear	Yes
Were withdrawals from the study explained?	Unclear[5]	Unclear[5]	Unclear[5]	Unclear[5]	Unclear[5]
VALID	Yes	Yes	Yes	Yes	Yes
RELEVANT	Yes	Yes	Yes	Yes	Yes

[1] Defined as <3 months.

[2] Reference standard=colonoscopy after segmental unblinding or second look colonoscopy

[3] Reference standard=colonoscopy followed by a second look colonoscopy if there was no match for polyps >9 mm on CT-colonography

[4] Of the 2,600 subjects recruited, 69 subjects were excluded in the analysis as a consequence of incomplete colonoscopy and/or CT-colonography results, not further specified.

[5] In none of the studies was explained whether there were any withdrawals from the study.

Appendix 2

Table 5 CT-colonography imaging characteristics

Author	Preparation, including dietary restrictions*	Tagging*	Branch name and type of scanner	Bowel distension, manual or automatic	Spasmolytical drugs	Technical aspect
Graser, 2009 [26]	Extensive: 4 L PEG 4×5 mg bisacodyl 30 ml sodiumphosphate Clear liquid diet	50 ml iopamidol	Siemens Somaton Sensation, multislice: 64	Both: 74% automated CO2 insufflation 26% manual room air insufflation	butylscopolamin 20 mg/mL i.v.	Supine and prone; Collimation 0.6 mm; Slice thickness 0.75 mm; Reconstruction interval 0.5 mm; Tube voltage 120 kVp; Ref 70mAs supine (3.2 mSv) and 30mAs prone (1.3 mSv)
Johnson, 2008 [27]	Extensive: 10 mg bisacodyl (or current institutional standard) combined with - PEG in 42% - sodiumphosphate in 54% - magnesium citrate in 4% OR other substances in <1% Diet depended on daily practice in each participating center	barium sulfate in 4% OR iodinated contrast in 1% OR both in 94% OR neither indicated in 1%	Siemens (58%), GE (34%), Philips (4%), Toshiba (4%) Multislice: 16 slice in 47% 40 slice in 4% 64 slice in 50%	Both: automated CO2 insufflation was used primarily, if colonic insufflation was inadequate, manual insufflation of room air was used	92% glucagon 1 mg s.c. 7–15 min before examination	Supine and prone; Collimation 0.5–1.0 mm; Slice thickness 1.0–1.25 mm; Reconstruction interval 0.8 mm; Peak voltage 120 kV; 50 effective mAs
Kim, 2008 [28]	Extensive, based on participant's preference: - 4 L PEG in 71% - 90 mL sodiumphosphate 29% All subjects received 10 mg bisacodyl the day before the procedure and 20 mg bisacodyl 1 h before CTC Low-residue diet	No, i.v. 150 mL iopromide	Siemens Somaton Sensation, multislice: 16	Manual room air insufflation	No	Supine and prone; Collimation 2.0 mm; Slice thickness 2.0 mm; Reconstruction interval 1.0 mm; Tube voltage 120 kVp; 50 effective mAs prone, 120 effective mAs supine

Macari, 2004 [29]	Limited: 2×45 mL phosphosoda on the day prior to the study Diet not specified	Not specified	Siemens Plus 4 Volume Zoom, Multislice: 4	Manual room air insufflation (minimum of 40 puffs)	Not specified	Supine and prone; Collimation 4x1mm; Slice thickness 1.25 mm; Reconstruction interval 1 mm; Tube voltage 120 kVp; 50 effective mAs
Pickhardt, 2003 [30, 31]	Limited: 90 mL sodium phosphate 10 mg bisacodyl Clear liquid diet	500 mL of barium (2.1%) 120 mL diatrizoate meglumine and diatrizoate sodium	GE Lightspeed or LightSpeed Ultra, Multislice: 4 or 8	Manual room air insufflation	Not specified	Supine and prone; Collimation 1.25–2.5 mm; Slice thickness unclear; Reconstruction interval of 1 mm; Tube voltage 120kVp; 100 mAs

Appendix 3

Table 6 Characteristics of readers and reference standard

Author	CTC readers, experience	CTC reading strategy	CTC report	Endoscopists	Measurement of polyp (OC)	Segmental unblinding (SU) or second look colonoscopy (SLC)	Histopathology	CTC lesion tP compared to colonoscopy	Reference standard
Graser, 2009 [26]	3 abdominal radiologist, >300 CTC examinations	primary 3D (2D problem solving)	Location Size 2D	6 gastroenterologists >1,000 colonoscopies	open biopsy forceps	SU, directly SLC	Yes	same/adjacent segment and size category	colonoscopy results after segmental unblinding
Johnson, 2008 [27]	15 radiologists, >500 CTC examinations or 1.5 day training session, with detection rate ≥90% for polyps ≥10 mm (qualifying examination)	at random: 50% primary 2D (3D problem solving) 50% primary 3D (2D problem solving)	Location Size 2D Only lesions ≥5 mm reported Degree of diagnostic confidence	performed or directly supervised by an experienced gastroenterologist (information regarding experience not collected)	determined from pathology report unless not completely resected, then colonoscopy-derived estimates were used	SLC <90 days if lesions >9 mm were detected on CTC	Yes	one or more lesions met the criteria for size (6–9 mm or >9 mm) identified	colonoscopy +/− SLC +histopathology
Kim, 2008 [28]	2 abdominal radiologist, >100 CTC examinations	primary 2D (3D problem solving)	Location Size 2D Morphology	5 gastroenterologists >3,000 colonoscopies	open biopsy forceps	SU, directly SLC	Yes	same/adjacent segment, size of lesions should be at least <50% margin of error, similar morphology	*Per patient*: histopathology (all polyps resulting OC +SU) *Per polyp*: colonoscopy after segmental unblinding
Macari, 2004 [29]	1 radiologist, 5 years CTC reading experience	primary 2D (3D problem solving)	Location Size (not specified) Morphology	1 gastroenterologist with 5 years experience and 1 GE fellow with direct supervision	open biopsy forceps	None	Yes	same/adjacent segment, size difference ≤3 mm, similar morphology	colonoscopy without knowledge of CTC findings
Pickhardt, 2003 [30, 31]	6 radiologists, ≥25 CTC examinations	primary 3D (2D problem solving)	Location Size 3D Morphology Degree of diagnostic confidence	14 gastroenterologists 3 colorectal surgeons Several years experience	calibrated linear probe	SU, directly SLC if finding on CTC ≥5 mm	Yes	same/adjacent segment, size of lesions should be at least <50% margin of error	colonoscopy results after segmental unblinding

Appendix 4

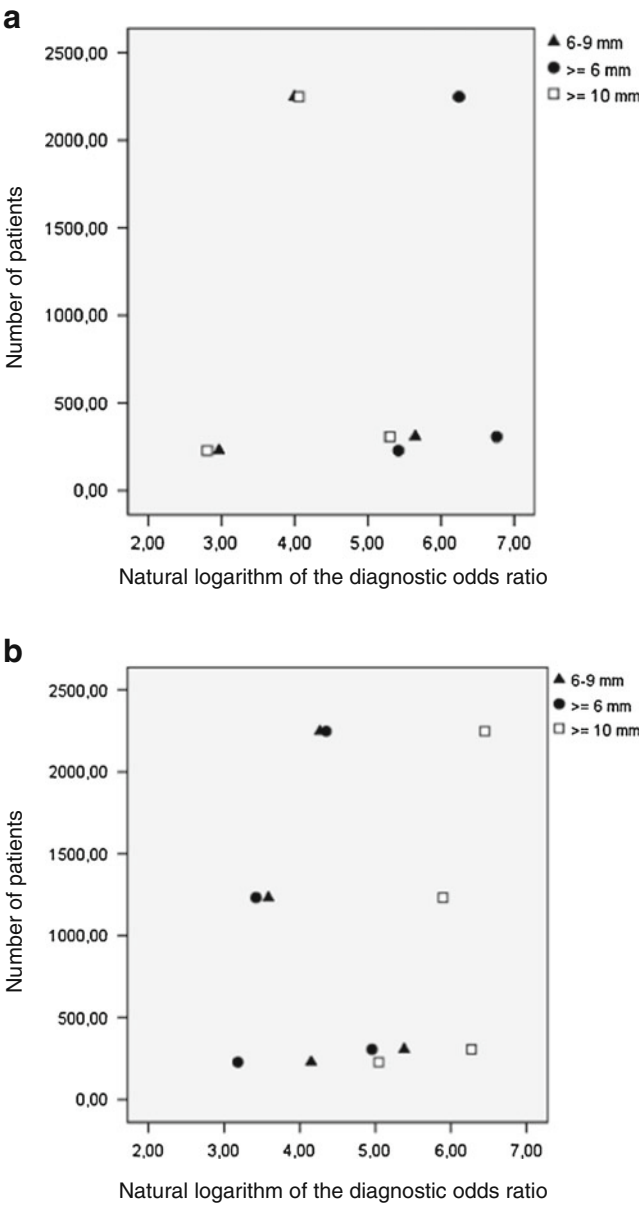

Fig. 4 **a** Funnel plot per patient, all polyps, **b** Funnel plot per patient, adenomas

Appendix 5

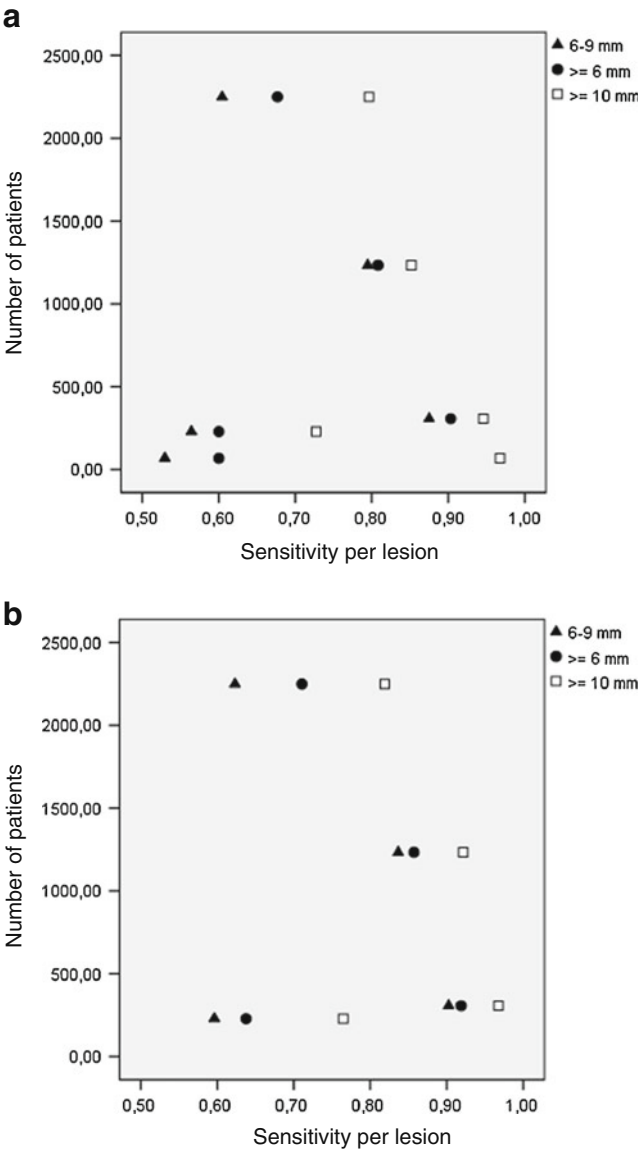

Fig. 5 **a** Funnel plot per polyp, all polyps, **b** Funnel plot per polyp, adenomas

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