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

Margriet C. de Haan · Rogier E. van Gelder · Anno Graser · Shandra Bipat · Jaap Stoker

Received: 14 November 2010/Revised: 1 February 2011/Accepted: 3 February 2011/Published online: 1 April 2011
© The Author(s) 2011. This article is published with open access at Springerlink.com

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). I²-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

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
specificity values for the following type of lesions: all polyps, adenomatous polyps, advanced adenomas (defined as an adenoma with $>25\%$ villous features, size $\geq 10\ mm$ 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: $6–9\ mm$, $\geq 6\ mm$ and $\geq 10\ mm$, 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 (= $(TP \times TN)/(FN \times FP)$). 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 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 CO₂ 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 spasmyotical drug was administered [28], it was not specified whether spasmyotical 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 \(\geq 10\) 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<sup>a</sup> | 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 | 171:140 | 60.5                     |
| Johnson, 2008 [27] | Multi (n=15), prospective                         | ≥50 year asymptomatic<sup>b</sup> | 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 | Included in analysis: 307 | 1088:1161 | 58.0                     |
| Kim, 2008 [28] | Single, prospective                              | ≥50 year asymptomatic<sup>c</sup> | 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                     |
| 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                         |
| Pickhardt, 2003 [30, 31] | Multi (n=4), prospective                        | 50–79 year asymptomatic<sup>d</sup> | 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 | 728:505 | 57.8                     |

<sup>a</sup> asymptomatic=free of symptoms of colonic diseases such as melena, haematochezia, diarrhoea, relevant changes in stool frequency or abdominal pain

<sup>b</sup> asymptomatic=no melena, anemia or hematochezia more than ones last 6 months, no lower abdominal pain

<sup>c</sup> asymptomatic=no significant GI signs or melena, haematochezia, iron-deficiency anemia, weight loss or abdominal pain within 6 months before study

<sup>d</sup> 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 I² 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 mm | ≥10 mm |
|----------------|-----------------------|-------|--------|
|                | 6–9 mm                | 6–9 mm| 6–9 mm |
| Graser [26]    | 25                     | 50    | 25     |
| Johnson [27]   | 78                     | 156   | 78     |
| Kim [28]       | 23                     | 36    | 13     |
| Macari [29]    | n.a.                  | n.a.  | n.a.   |
| Estimated sensitivity | 68.1 (52.9–80.2) | 75.9 (62.3–85.8) | 83.3 (76.8–89.0) |
| F² heterogeneityᵃ | 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) |
| F² heterogeneityᵃ | 83.7% (61.7–93.1) | 90.4% (78.5–95.7) | 60.1% (15.2–81.2) |

**Adenomatous polyps (n=4,018)**

|                | All polyps (n=4,018) | ≥6 mm | ≥10 mm |
|----------------|-----------------------|-------|--------|
|                | 6–9 mm                | 6–9 mm| 6–9 mm |
| Graser [26]    | 19                    | 42    | 23     |
| Johnson [27]   | 62                    | 137   | 75     |
| Kim [28]       | 22                    | 31    | 9      |
| Pickhardt [30, 31] | 104                | 149   | 45     |
| Estimated sensitivity | 78.6 (66.1–87.3) | 82.9 (73.6–89.4) | 87.9 (82.1–92.0) |
| F² heterogeneityᵃ | 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) |
| F² heterogeneityᵃ | 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 mmᵃ | Colorectal cancerᵇ sensitivity | Advanced neoplasia ≥6 mmᵇ sensitivity |
|----------------|--------------------------|-------------------------------|-------------------------------------|
| Graser [26]    | 92.6%                    | 100%                          | 92.9%                               |
| Johnson [27]   | 83.3%                    | 100%                          | 84.0%                               |
| Kim [28]       | 87.5%ᵇ                   | 100%                          | 88.2%ᵇ                              |

ᵃIf F² values of sensitivity and/or specificity were larger than 25%, data were considered as significantly heterogeneous
ᵇNo lesions <6 mm found
ᶜNot 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) | Adenomatous polyps (n=4,018 participants) | Advanced adenomas (n=2,785 participants) | Colorectal cancer (n=2,785 participants) | Advanced neoplasia (n=2,785 participants) |
|----------------------|-----------------------------------|-------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
|                      | 6–9 mm                            | ≥6 mm                                     | ≥10 mm                                   | 6–9 mm                                   | ≥6 mm                                   | ≥10 mm                                   |
|                      | TP/FN                             | TP/FN                                     | TP/FN                                    | TP/FN                                    | TP/FN                                    | TP/FN                                    |
| Graser [26]          | N=307                             | 49/7                                      | 84/9                                     | 35/2                                     | 2                                       |
| Johnson [27]         | N=2,249                           | 113/74                                   | 203/97                                   | 90/23                                    | 6                                       |
| Kim [28]             | N=229                             | 44/34                                     | 60/40                                    | 16/6                                     | 0                                       |
| 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   |                                   |                                           |                                          |                                          |                                          |
|                      | 88.6% (77.8–94.2)                 | 89.3% (79.3–94.4)                         | 33.3% (0.0–56.9)                         |                                          |                                          |
| Graser [26]          | N=307                             | 37/4                                      | 67/6                                     | 30/2                                     | 2                                       |
| Johnson [27]         | N=2,249                           | 81/49                                    | 167/68                                   | 86/19                                    | 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   |                                   |                                           |                                          |                                          |                                          |
|                      | 88.5% (75.9–94.5)                 | 89.2% (77.7–94.8)                         | 44.9% (2.8–68.8)                         |                                          |                                          |
| Not possible to calculate estimated sensitivity due to small numbers |

Not possible to calculate estimated sensitivity due to small numbers

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
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).
**Adenomas** Estimated sensitivities for adenomas $\geq 6$ mm and $\geq 10$ mm were 80.0% (95% CI 66.9–88.7) and 85.9% (95% CI 80.4–90.0), corresponding estimated specificities 91.4 (84.1–95.5) and 97.6 (95.0–98.9).

**Advanced adenomas** Estimated sensitivities for advanced adenomas $\geq 6$ mm and $\geq 10$ 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.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

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? | 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? | No2 | No, partly3 | No2 | Yes | No2 |
| 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, partly4 | Unclear | Unclear | Yes |
| Were withdrawals from the study explained? | Unclear5 | Unclear5 | Unclear5 | Unclear5 | Unclear5 |
| 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.
| Author             | Preparation including dietary restrictions* | Tagging* | Branch name and type of scanner | Spasmolytical drugs | Technical aspect |
|--------------------|---------------------------------------------|----------|---------------------------------|---------------------|------------------|
| Graser, 2009 [26]  | Extensive: 50 ml iopamidol                   | 50 ml iopamidol | Siemens Somaton Sensation, multislice: 64 | Both: butylscopolamin 20 mg/mL i.v. | Tube voltage 120 kV; Ref 70mA, supine (3.3 mSv) and 50mA prone (1.3 mSv); Slice thickness 0.75 mm; Collimation 0.6 mm; Reconstruction interval 0.5 mm; Supine and prone; Clear liquid diet Tube voltage 120 kV; Slice thickness 0.75 mm; Collimation 0.6 mm; Reconstruction interval 0.5 mm; 4 L PEG 74% automated CO2 insufflation |
| Johnson, 2008 [27]| Extensive: 4 L PEG                          | 4-5 mg bisacodyl | Siemens (58%), GE (34%), Philips (4%), Toshiba (4%) | Both: automated CO2 insufflation was used primarily, if colonic insufflation was inadequate, manual air insufflation of room air was used | Tube voltage 120 kV; Slice thickness 1.0–1.25 mm; Collimation 0.5–1.0 mm; Reconstruction interval 0.8 mm; 92% glucagon Supine and prone; 10 mg bisacodyl (or current institutional standard) combined with iodinated contrast in 1% OR 42% PEG in 94% OR 40 slice in 1% |
| Kim, 2008 [28]    | Extensive, based on participant’s preference: | No        | Siemens Somaton Sensation, multislice: | No i.v. 150 mL iopromide | Tube voltage 120 kV; Slice thickness 1.0 mm; Collimation 2.0 mm; Reconstruction interval 1.0 mm; 50 effective mAs Supine and prone; 50 effective mAs prone, 120 effective mAs supine |
| Author          | Year | Preparation, including dietary restrictions* | Tagging* | Branch name and type of scanner | Bowel distension, manual or automatic | Spasmolytical drugs | Technical aspect                                                                 |
|-----------------|------|---------------------------------------------|----------|---------------------------------|---------------------------------------|---------------------|-----------------------------------------------------------------------------------|
| 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 4x1 mm; 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 120 mL diatrizoate meglumine and diatrizoate sodium | 500 mL of barium (2.1%) | 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 |
### 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) | 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 | 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 | 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
References

1. McFarland EG, Levin B, Lieberman DA, Pickhardt PH, Johnson CD, Glick SN, Brooks D, Smith RA (2008) American Cancer Society; U.S. Multisociety Task Force on Colorectal Cancer; American College of Radiology. Revised colorectal screening guidelines: joint effort of the American Cancer Society, U.S. Multisociety Task Force on Colorectal Cancer, and American College of Radiology. Radiology 248:717–720

2. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD, Levin TR, Pickhardt PJ, Rex DK, Smith RA, Thorson A, Winawer SJ (2008) American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 134:1570–1595

3. Allen JD, Barlow WE, Duncan RP, Egede LE, Friedman LS, Keating NL, Kim P, Lave Jr, Laveist TA, Ness RB, Optican RJ, Steinwachs D, Vignir BA (2010) NIH state-of-the-science conference statement: enhancing use and quality of colorectal cancer screening. NIH Consens State Sci Statements 27

4. Sung JI, Lau JY, Young GP, Sano Y, Chiu HM, Byeon JS, Yeoh KG, Goh KL, Solano J, Rerknimitr R, Matsuda T, Wu KC, Ng S, Leung SY, Makharda G, Chong VH, Ko KY, Brooks D, Lieberman DA, Chan FK (2008) Asia Pacific Working Group on Colorectal Cancer. Asia Pacific consensus recommendations for colorectal cancer screening. Gut 57:1166–1176

5. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM (2009) American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening. Am J Gastroenterol 104:739–750

6. Ossoa J, Morrin MM, Kruskal JB, Lavin PT, Rosen MP, Raptopoulos V (2003) CT colonography of colorectal polyps: a metaanalysis. AJR Am J Roentgenol 181:1593–1598

7. Mulhall BP, Veenapan GR, Jackson JL (2005) Meta-analysis: computed tomographic colonography. Ann Intern Med 142:635–650

8. Halligan S, Altman DG, Taylor SA, Mallett S, Deeks J, Bartram CI, Atkin W (2005) CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 237:893–904

9. Rosman AS, Korsten MA (2007) Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. Am J Med 120:203–210

10. Chaparro M, Gisbert JP, Del Campo L, Cantero J, Mate J (2009) Accuracy of computed tomographic colonography for the detection of polyps and colorectal cancer tumors: a systematic review and meta-analysis. Digestion 80:1–17

11. Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, Woolf SH, Glick SN, Ganiats TG, Bond JH, Rosen L, Zapka JG, Olsen SJ, Giardiello FM, Sisk JE, Van Antwerp R, Brown-Davis C, Marciniak DA, Mayer RJ (1997) Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 112:594–642

12. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J (2003) The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 3:25

13. Winawer SJ, Zauber AG (2002) The advanced adenoma as the primary target of screening. Gastrointest Endosc Clin N Am 12:1–9

14. Iafrate F, Hassan C, Pickhardt PJ, Pichi A, Stagnitti A, Zullo A, Di Giulio E, Laghi A (2010) Portrait of a polyp: the CTC dilemma. Abdom Imaging 35:49–54

15. Bond JH (1993) Polyp guideline: diagnosis, treatment, and surveillance for patients with nonfamilial colorectal polyps. The Practice Parameters Committee of the American College of Gastroenterology Ann Intern Med 119:836–843

16. Lieberman D, Moravec M, Holub J, Michaels L, Eisen G (2008) Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. Gastroenterology 135:1100–1105

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560

18. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH (2005) Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 58:982–990

19. Arnesen RB, von Benzon E, Adamsen S, Svendsen LB, Raaschou HO, Hansen OH (2007) Diagnostic performance of computed tomography colonography and colonoscopy: a prospective and validated analysis of 231 paired examinations. Acta Radiol 48:831–837

20. Fidler JL, Johnson CD, MacCarty RL, Welch TJ, Hara AK, Harmsen WS (2002) Detection of flat lesions in the colon with CT colonography. Abdom Imaging 27:292–300

21. Wessling J, Domagk D, Lugering N, Schierhorn S, Heindel W, Domschke W, Fischbach R (2005) Virtual colonography: identification and differentiation of colorectal lesions using multi-detector computed tomography. Scand J Gastroenterol 40:468–476

22. Rex DK, Vining D, Kopecky KK (1999) An initial experience with screening for colon polyps using spiral CT with and without CT colonography (virtual colonoscopy). Gastrointest Endosc 50:309–313

23. Pineau BC, Paskett E, Chen GJ, Espeland MA, Philips K, Han JP, Mikulaninec C, Vining DJ (2003) Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. Gastroenterology 125:304–310

24. Iannaccone R, Laghi A, Catalano C, Brink JA, Mangiapane F, Trenna S, Piccentini F, Passariello R (2003) Detection of colorectal lesions: lower-dose multi-detector row helical CT colonography compared with conventional colonoscopy. Radiology 229:775–781

25. An S, Lee KH, Kim YK, Park SH, Kim HY, Kim SH, Kim N (2008) Screening CT colonography in an asymptomatic average-risk Asian population: a 2-year experience in a single institution. Am J Roentgenol 191:W100–W106

26. Graser A, Stieber P, Nagel D, Schäfer C, Horst D, Becker CR, Nikolau K, Lottes A, Geißbüscher S, Kramer H, Wagner AC, Diepolder H, Schirra J, Roth HJ, Seidel D, Göke B, Reiser MF, Kölligs FT (2009) Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 58:241–248

27. Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, Menias CO, Siewert B, Cheevert BH, Obremon RG, Fidler JL, Zimmerman P, Horton KM, Coakley K, Iyer RB, Hara AK, Halvorsen RA Jr, Casola G, Yee J, Herman BA, Burgart L, Limburg PJ (2008) Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 359:1207–1217

28. Kim YS, Kim N, Kim SH, Park MJ, Lim SH, Yim JY, Cho KR, Kim SS, Kim DH, Eun HW, Cho KS, Kim JH, Choi BI, Jung HC, Song IS, Shin CS, Cho SH, Oh BH (2008) The efficacy of intravenous contrast-enhanced 16-mrad detector CT colonography for detecting patients with colorectal polyps in an asymptomatic population in Korea. J Clin Gastroenterol 42:791–798
29. Macari M, Bini EJ, Jacobs SL, Naik S, Lui YW, Milano A, Rajapaksa R, Megibow AJ, Babb J (2004) Colorectal polyps and cancers in asymptomatic average-risk patients: evaluation with CT colonography. Radiology 230:629–636
30. Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, Wong RK, Nugent PA, Mysliwiec PA, Schindler WR (2003) Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 349:2191–2200
31. Pickhardt PJ, Choi JR, Hwang I, Schindler WR (2004) Non-adenomatous polyps at CT colonography: prevalence, size distribution, and detection rates. Radiology 232:784–790
32. Pickhardt PJ, Lee AD, Taylor AJ, Michel SJ, Winter TC, Shadid A, Meiners RJ, Chase PJ, Hinshaw JL, Williams JG, Prout TM, Husain SH, Kim DH (2007) Primary 2D versus primary 3D polyp detection at screening CT colonography. AJR Am J Roentgenol 189:1451–1456
33. De Vries AH, Liedenbaum MH, Bipat S, Truyen R, Serlie IW, Cohen RH, van Elderen SG, Heutinck A, Kesselring O, de Monyé W, te Strake L, Wiersma T, Stoker J (2009) Primary uncleaned 2D versus primary electronically cleansed 3D in limited bowel preparation CT-colonography. Is there a difference for novices and experienced readers? Eur Radiol 19:1939–1950
34. Howson, Colin, Peter Urbach (1993) Scientific reasoning: The Bayesian approach. Open Court
35. Van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E (2006) Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 101:343–350