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SYSTEMATIC REVIEW

Comparison of the participation rate between CT colonography and colonoscopy in screening population: a systematic review and meta-analysis of randomized controlled trials

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Objective: To compare the participation rate between CT colonography (CTC) and colonoscopy in screening population in randomized controlled trials (RCTs).

Methods: A search was performed using the PubMed, Web of Science, and Cochrane databases. RCTs that included screening populations and reported participation number were assessed. Cochrane risk of bias tool was used to assess the bias and quality. Risk ratio (RR) was used to present the results. The non-participation rate was analyzed to verify the results of participation rate.

Results: Five of 760 studies, with a total of 15,974 invitees, were included. The participation rate was higher at CTC (28.8%) than colonoscopy (20.8%), although the difference did not reach statistical significance (RR = 1.26; $p = 0.070$; $I^2 = 90.3\%$). The non-participation rate at CTC was significantly lower than colonoscopy (RR = 0.92; $p = 0.012$; $I^2 = 86.7\%$). Subgroup analysis

suggested both the participation and non-participation rate were with significant difference between reduced/no cathartic preparation CTC and colonoscopy. Cumulative meta-analysis showed both the participation rate and non-participation rate exhibited a trend over time and sample size.

Conclusion: The participation rate was higher at CTC than colonoscopy, although the difference did not reach statistical significance. But the non-participation rate was with statistical difference. Screening population seemed more likely to participate the reduced/no cathartic preparation CTC. Statistical evidence was provided for more large RCTs are needed in the future.

Advances in knowledge: The screening populations seem more likely to participate in the CTC, especially the reduced/no cathartic preparation CTC. The statistical evidence was provided for more large RCTs are needed in the future.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide, and the incidence and mortality rates of CRC are rapidly rising in many low- and middle-income countries.^{1,2} Several studies have suggested that the incidence and mortality of CRC can be reduced by screening to facilitate the detection and removal of colorectal adenomas.^{3,4} Currently, with the development of technology, CT colonography (CTC) shows similar sensitivity to colonoscopy.⁵ And a meta-analysis suggested that CTC was inferior in detecting advanced colorectal

neoplasia compared to colonoscopy.⁶ Meanwhile, CTC and colonoscopy have both been recommended by the United States Preventive Services Task Force.⁷

Methods of screening and diagnosis are evaluated not only by their accuracy but also by their participation rates. Selection of screening methods that are accepted by many people is a focus in cancer screening programs worldwide. A meta-analysis published in 2011 suggested that the participation rate in the colonoscopy group was higher than that in the CTC group (28% in the colonoscopy group and 22% in the

CTC group).⁸ But it only included three studies in the comparison between CTC and colonoscopy, and two of them are randomized controlled trials (RCTs), and another one is non-RCT (a prospective study) without random assignment that might result in the selection bias in participation rates between two groups.⁹ CTC is increasingly used by patients and doctors for CRC screening because of its less invasive characteristics. Several RCTs with large sample sizes have been published in recent years. Moreover, a recent study reported greater acceptance of the preparation and examination procedures for reduced-laxative CTC than that for colonoscopy in the faecal immunochemical test (FIT)-positive patients.¹⁰ Therefore, we conducted a meta-analysis based on RCTs with the highest level of evidence in evidence-based medicine. A meta-analysis to compare the participation rates between CTC and colonoscopy will have clinical significance.

The primary purpose of this study was to systematically review RCTs to examine the participation rates of CTC and colonoscopy in CRC screening studies. The secondary purpose was to compare the non-participation rates between CTC and colonoscopy to verify the results of the participation rate. An additional aim was to estimate the trends of participation and non-participation rates with the accumulation of publication time and sample size, respectively.

METHODS AND MATERIALS

A review protocol was prepared in accordance with the Cochrane Handbook for Systematic Reviews (www.handbook.cochrane.org) and is available from the authors on request. The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement¹¹ for the reporting of systematic reviews and meta-analysis.

Search strategy

We searched the PubMed, Web of Science and the Cochrane Library databases for relevant articles. The date range for our literature searching is from the inception of the database to the 16 April 2019. The studies were limited to RCTs published in English. Synonyms for “CT colonography” such as colonography, colography, CTC, CT colonoscopy, CT pneumocolon, virtual colonoscopy, and virtual endoscopy were combined using the Boolean operator “OR”. A similar search strategy was used for “colonoscopy”. Both search results were combined using the Boolean operator “AND”. The MeSH terms “colonography CT” and “colonoscopy” were used when possible. The PubMed search strategy was as follows: (((((optical colonoscopy) OR colonoscopy)) AND ((((((colonography) OR colongraphy) OR CTC) OR CT colonoscopy) OR CT pneumocolon) OR virtual colonoscopy) OR virtual endoscopy))) OR ((“Colonography, Computed Tomographic”[MeSH]) AND “Colonoscopy”[MeSH]) with the following filter: Randomized Controlled Trial. The reference lists from the studies which were scored for validity and the identified review articles were manually searched to identify other relevant studies to be additional data.

Study selection

All abstracts of the primary studies were independently screened by two authors who excluded clearly ineligible studies. The full

texts of the potentially eligible studies were reviewed. Differences in opinions regarding eligibility were resolved by face-to-face consensus discussions. Besides, all inconsistencies were resolved by a third author if discrepancies occurred between the two screening authors. If the trial information was not fully reported in the articles, the protocols used in each study were searched and screened.

Inclusion and exclusion criteria

Studies meeting each of the following criteria were eligible: (1) RCTs published in English; (2) studies in which patients were randomly invited to undergo CTC or colonoscopy; and (3) studies in which the participation number was reported for the CTC and colonoscopy groups. Because flexible sigmoidoscopy (FS) is just a part of colonoscopy, studies comparing FS and CTC were excluded.

Data extraction

A standardized form was used to extract the following study details: authors, year of publication, country, age, study design, presence of cathartic preparation, and criterion for recommending colonoscopy. The analysis was based on the intention-to-treat (ITT) principle. The participation rate was defined as the proportion of participants undergoing screening among all invitees. In contrast, the non-participation rate was defined as the proportion of those population who were invited while finally did not participate in CRC screening. If the participants did not complete the test because of pain, bleeding etc., they were also included in the number of participants who were undergoing screening.

Quality assessment

Two authors assessed the quality of all included studies using the Cochrane risk of bias tool.¹² Cochrane risk of bias measures the risk of potential bias in studies along with five key domains: (1) selection bias, (2) performance bias, (3) detection bias, (4) attrition bias and (5) reporting bias. The risk of bias is judged as “low,” “high,” or “unclear.” The quality of included studies was assessed by Review Manager 5.3 software. Two authors performed the quality assessment independently and they were blinded to each other. All disagreements were resolved by discussion and referral to a third author for adjudication.

Statistical analysis

Stata 12.0 was used to analyze the data. Considering the burden of CTC and colonoscopy on patients, in general, the colonoscopy may be more invasive than CTC, and the bowel preparation causes more uncomfortable and for patients, which make the burdens and risks of colonoscopy may be heavier than CTC. So, the risk ratio (RR) was chosen to compare trials and assess the value of the screening method used. If the RRs were not reported in a study directly, they were calculated using the ratio of the respective rates for the CTC and colonoscopy groups. Because of the asymmetric nature of RR, the non-participation rate was also compared between CTC and colonoscopy to verify the results of the participation rate. All statistical tests were two-sided. Pooled estimates with 95% confidence intervals (CIs) were calculated using the weighted variance technique. The Higgins I² statistic

Figure 1. Flowchart depicting the search strategy. RCT, randomized controlled trial.

was used to determine the total variation across studies due to heterogeneity. If the I^2 statistic was $\leq 50\%$, the findings among the studies were considered homogeneous, and a fixed-effects model was used to pool studies; otherwise, a random-effects model was used. Subgroup analyses were based on bowel preparation. To assess trends with publication time and sample size, a regression-based generalized least squares (GLS) method was used in the cumulative meta-analysis.¹³ To determine whether any particular study skewed the results of this meta-analysis, we conducted a sensitivity analysis by excluding studies one by one in full cathartic preparation CTC group and reduced/no preparation CTC group and recalculating the results respectively to evaluate the stability of the results. An Egger linear regression test was used to evaluate the publication bias.

RESULTS

Search results

The initial search yielded 760 articles (Figure 1). After excluding duplicates and articles that did not match the inclusion criteria, 11 articles remained. The most frequent reasons for exclusion were the study design and use of methods not related to CTC or colonoscopy in the screening population. After assessment of the 11 full-text publications, 6 additional articles were excluded because their results were obtained from the same RCTs.^{14–19} Finally, five articles were included in this systematic review.^{20–24}

Study characteristics

The study characteristics are outlined in Table 1. Three studies were single-centre RCTs,^{20,23,24} and the remaining studies were multi-centre RCTs.^{21,22} Two studies conducted in Australia were community-based studies,^{20,21} and the others were population-based studies. Three studies included the asymptomatic and average-risk individuals, and not previously invited for screening for colorectal cancer.^{20–22} The other two studies did not mention the average-risk or high-risk participants.^{23,24} But both of them excluded individuals if they: had a history of colorectal cancer, adenoma, or inflammatory bowel disease; had undergone colonoscopy or fecal occult blood test (FOBT)/FIT before. In one study, participants were invited to participate by telephone,²⁰ and the others used invitation letters. None of the studies mentioned whether their population reliant on health insurance. Full bowel preparations were performed before all colonoscopies. Four studies used full bowel preparations before CTC.^{20,21,23} Non-cathartic CTC preparations were described in one study.²² One study examined two groups, including both reduced and full cathartic preparations.²⁴

The patient populations were all older than 50 years. The total study population included 15,974 invitees (8384 in the CTC group and 7590 in the colonoscopy group), and the largest population comprised 8844 invitees.²² All studies provided a clear

Table 1. Characteristics of the included studies and patients

Author	Year	Country	Sample type	Population risk	Sample size	Invitation methods	Age	Single/multicentre	Primary aim of the trial	Health insurance	Catharsis for CTC	Type of bowel preparation for colonoscopy
Scott et al ²⁰	2004	Australia	Community-based	Asymptomatic and average-risk	709	Telephone	≥50	Single	Participation and detection rate	Unknown	Full: same as colonoscopy	Polyethylene glycol 1 L and two sachets of PicoLax
MACS Group ²¹	2006	Australia	Community-based	Asymptomatic and average-risk	429	Letters	≥50	Multi	Participation and detection rate	Unknown	Full: same as colonoscopy	Polyethylene glycol 1 L and two sachets of PicoLax
Sloop et al ²²	2012	Netherlands	Population-based	Asymptomatic and average-risk	8844	Letters	≥50	Multi	Participation and detection rate	Unknown	No	Polyethylene glycol 2L and transparent fluid 2L and low-fibre diet 2 days
You et al ²³	2015	Canada	Population-based	Not mentioned but excluded the high-risk population	131	Letters	≥50	Single	Participation and detection rate	Unknown	Full: same as colonoscopy	Four 5 mg tablets of bisacodyl, one sachet of sodium picosulfate 10 mg, magnesium oxide 3.5 g and citric acid 12 g dissolved in 150 ml of water, and drinking at least 1 L; a second sodium picosulfate sachet dissolved in 150 ml of water and drank at least 1 L of clear fluid at bedtime
Sali et al ²⁴	2016	Italy	Population-based	Not mentioned but excluded the high-risk population	5861	Letters	≥54	Single	Participation and detection rate	Unknown	Reduced: 13.8g of macrogol 3350 diluted in a glass of water at the three main meals for three days before the examination. Full: the same as colonoscopy	Solution of polyethylenglycole 2L, followed by clear liquid 2L administered in split-dose the day before and the day of the examination

CTC: CT colonography; MACS: Multicentre Australian Colorectal-neoplasia Screening.

Table 2. Results of participation rate for the included studies

	CTC		Colonoscopy	
	No. of invitees	No. of participants (%)	No. of invitees	No. of participants (%)
Scott et al ²⁰	359	65 (18.1)	350	57 (16.3)
MACS group ²¹	215	35 (16.3)	214	38 (17.8)
Stoop et al ²²	2920	982 (33.6)	5924	1276 (21.5)
You et al ²³	65	50 (76.9)	66	53 (80.3)
Sali et al ²⁴	4825 (2395 for r-CTC, 2430 for f-CTC)	1286 (26.7) (674 for r-CTC, 612 for f-CTC)	1036	153 (14.8)
Total events	8384	2418 (28.8)	7590	1577 (20.8)

CTC: CT colonography; MACS: Multicentre Australian Colorectal-neoplasia Screening; r-CTC: reduced-CT colonography; f-CTC: full-CT colonography

description of the patient characteristics and the inclusion and exclusion criteria.

Study quality

According to the Cochrane risk of bias tool, all of the studies obtained a low risk in general, especially in performance bias, detection bias, and reporting bias. The allocation method is not concealed in two studies.^{22,23} One study did not mention whether it used the allocation concealment.²¹ None of the five studies used blinding methods. According to the Cochrane risk of bias tool, it can be assessed as “low risk of bias” if “no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding.” Because the outcome of our study is to compare the participation rate and non-participation rate, participants or non-participants can’t be blinded. So we judge lacking blinding as “low risk of bias.” One study asked for consent before randomizing means their participation rate is likely to be proportionally much higher than the other studies, so it might with the potential risk of other bias.²³ And this study was stopped early due to lack of funding, so it is judged as high risk of attrition bias.²³ Supplemental Figure a and b shows the risk of bias of all included studies.

Outcomes of the comparison for participation rate and non-participation rate

Tables 2 and 3 showed the outcomes from the included studies. The participation rate was higher at CTC (2418/8384, 28.84%)

than colonoscopy (1577/7590, 20.78%), although the difference did not reach statistical significance (RR = 1.264; 95% CI: 0.981 to 1.630; $p = 0.070$; $I^2 = 90.3\%$, Figure 2a). But non-participation rate at CTC was significantly lower than colonoscopy (RR = 0.915; 95% CI: 0.855 to 0.981; $p = 0.012$; $I^2 = 86.7\%$, Figure 2b).

Subgroup analysis was performed for different kinds of cathartic preparation. The participation rate in full cathartic preparation CTC was slightly higher than that in colonoscopy (RR = 1.15; 95% CI: 0.79 to 1.68; $p = 0.462$; $I^2 = 90.0\%$), and as for the reduced/no cathartic preparation CTC, the participation rate was significantly higher than colonoscopy (RR = 1.70; 95% CI: 1.40 to 2.07; $p < 0.001$; $I^2 = 80.5\%$, Figure 3a).

In contrast, the non-participation rate in full cathartic preparation CTC group was slightly lower than colonoscopy group (RR = 0.95; 95% CI: 0.87 to 1.05; $p = 0.332$; $I^2 = 81.1\%$), and the difference was also with statistical significance between reduced/no cathartic preparation CTC and colonoscopy (RR = 0.85; 95% CI: 0.83 to 0.86; $p < 0.001$; $I^2 = 0.0\%$, Figure 3b).

Additionally, when the two studies with the risk of bias was excluded,^{22,23} both the difference of participation rate and non-participation rate between CTC and colonoscopy did not reach statistic significant (Participation rate: RR = 1.26; 95% CI: 0.81 to 1.96; $p = 0.302$; $I^2 = 85.7\%$; Non-participation rate: RR = 0.95; 95% CI: 0.84 to 1.06; $p = 0.327$; $I^2 = 90.8\%$).

Table 3. Meta-analysis of participation rate and non-participation rate for all included studies

	Participation rate			Non-participation rate		
	RR	95% CI		RR	95% CI	
Scott et al ²⁰	1.112	0.804	1.537	0.978	0.915	1.046
MACS group ²¹	0.917	0.603	1.393	1.018	0.934	1.109
Stoop et al ²²	1.561	1.455	1.675	0.846	0.822	0.871
You et al ²³	0.958	0.801	1.146	1.172	0.606	2.265
Sali et al ²⁴	1.805	1.548	2.104	0.861	0.835	0.887
Pooled results	1.264	0.981	1.630	0.915	0.855	0.981

CTC: CT colonography; MACS: Multicentre Australian Colorectal-neoplasia Screening; RR: Risk Ratio; 95% CI: 95% Confidence Intervals

Figure 2 (a):Pooled results of the participation rates for CTC and colonoscopy in all included studies. (b):Pooled results of non-participation rates for CTC and colonoscopy in all included studies. CTC, CT colonography; MACS, Multicentre Australian Colorectal-neoplasia Screening

Cumulative meta-analysis and trend detection over time and sample size

To assess the influence of the publication year and sample size, a cumulative meta-analysis was performed. [Supplemental Figure c and d](#) showed that with the accumulation of publication time and sample size, the participation rate of CTC had a trend of higher than colonoscopy, and the non-participation rate suggested a trend towards to the colonoscopy. When the trend detection was conducted, the results indicated the participation rate exhibited a possible trend with publication time (all studies: Coef. = 0.042, $p < 0.001$, excluding the first study: Coef. = 0.082, $p < 0.001$) and sample size (all studies: Coef. = 0.066, $p < 0.001$, excluding the first study: Coef. = 0.154, $p < 0.001$). The non-participation rate, in contrast, also suggested a trend of publication time (all studies: Coef. = -0.021, $p < 0.001$, excluding the first study: Coef. = -0.039, $p < 0.001$) and sample size (all studies: Coef. = -0.039, $p < 0.001$, excluding the first study: Coef. = -0.040, $p < 0.001$).

Sensitivity analyses

Because there were only two studies included in reduced/no cathartic preparation CTC group, it is not necessary to take a sensitivity analysis, but the sensitivity analysis in full cathartic preparation CTC subgroup showed that no matter the participation rate or the non-participation rate, the results did not change significantly when we excluded any a study one by one. And for both the participation rate and non-participation rate, the I^2 reduced to 0.0% when the study by Sali et al was excluded²⁴ ([Supplemental Table](#)).

Other analysis

According to the Egger linear regression test, no publication bias was observed for the participation rate among the included studies ($p = 0.271$, 95% CI: -10.5-4.26). In contrast, the non-participation rate also did not exhibit publication bias ($p = 0.139$, 95% CI: -1.96-8.59).

Figure 3 (a): Subgroup analysis of the participation rates for full or reduced/no cathartic preparation CTC and colonoscopy. (b): Subgroup analysis of non-participation rates for full or reduced/no cathartic preparation CTC and colonoscopy. CTC, CT colonography; MACS, Multicentre Australian Colorectal-neoplasia Screening.

a

b

DISCUSSION

This systematic review and meta-analysis showed that the participation rate was higher at CTC than colonoscopy, although the difference did not reach statistical significance. In contrast, the non-participation rate in CTC was significantly lower than colonoscopy. The screening populations seem more likely to participate in the reduced/no cathartic preparation CTC over the full cathartic preparation. Both the participation and non-participation rate showed a trend with publication time and sample size.

Our study found the participation rate in the CTC group (28.84%) was higher than that in the colonoscopy group (20.78%) although the difference was not with statistical significance. Actually, the *p*-value of participation rate was 0.07, which was very close to 0.05, so we cannot draw an absolute conclusion that there was no difference between CTC and colonoscopy. Moreover, the non-participation rate between the two groups was with statistical significance based on the asymmetric nature of RR. This participation rate was similar to a previous meta-analysis that only included three studies.⁶ However, our results were completely different from a previous study published in 2011 which showed participation rates were of 28% for colonoscopy and 22% for CTC.⁸ Data from the Colonoscopy or Colonography for Screening trial showed that the most common reason for non-participation to screening colonoscopy was the unpleasant experience for the procedure.¹⁵ Another study showed that people prefer less invasive tests over more sensitive tests in screening program.²⁵ Moreover, studies have increasingly demonstrated that CTC has high sensitivity and a high detection rate for CRC and neoplasia.^{5,26}

The bowel preparation was reported to be one of the most frequent reasons for non-attendance to screening CTC in the Colonoscopy or Colonography for Screening Study.¹⁵ Our sub-analysis also showed that the participation rate in reduced/no cathartic CTC group was significantly higher than colonoscopy group and the non-participation rate in reduced/no cathartic CTC was also significantly lower than colonoscopy. There were several studies suggested that the discomfort and difficulty from bowel preparation make the reduced/no cathartic CTC more acceptable.^{10,27} A survey conducted in England also revealed that the intention for undergoing no-cathartic preparation CTC was rated more positively than that for full-cathartic preparation CTC.²⁸ And more populations have increased intention to repeat reduced cathartic CTC because of better tolerability, lower interference, and fewer/milder gastrointestinal symptoms according to SAVE study.²⁹ For colonoscopy, an RCT comparing the participation rate of full-volume and reduced-volume cathartic preparation, but the low-volume bowel preparation did not improve participation rate.³⁰ The risk of bleeding and perforations, which are the major complications of colonoscopy, may explain why patients are more likely to undergo CTC than colonoscopy.³¹ Additionally, the number of non-participant was higher than participant in both CTC and colonoscopy, which meant that most population seemed not likely to participate in CRC screening, so both CTC and colonoscopy should improve themselves regarding the reasons for non-participation.

Another factor that may influence the participation rates for CTC and colonoscopy may be the cost. A study showed that CTC cost up to 50% less than colonoscopy for CRC testing, particularly for patients with commercial health insurance.³² Other studies also found that because of the higher participation rates, CTC screening is more cost-effective than colonoscopy screening for CRC.^{19,33,34} However, the latest meta-analysis showed that the performance of colonoscopy every 10 years was less costly than other common strategies used in the United States.³⁵ Additionally, clinical doctors must consider the screening process. Once CTC identifies a positive lesion, the patient is recommended to undergo colonoscopy or a biopsy via polypectomy. Therefore, the resulting cost becomes much higher than the cost to undergo an initial colonoscopy because colonoscopy may allow direct biopsy and polypectomy. And in our study, none of the studies mentioned whether their population reliant on health insurance. So, more in-depth studies comparing costs are needed in the future.

The cumulative meta-analysis suggested both the participation and non-participation rate exhibit a trend with the publication time and sample size, which means that the participation rate may finally achieve statistic significance with more large RCTs published in the future. Based on the results that the non-participation rate had been with the statistic significance, the current non-significant results of participation rate might be limited by the small number of included studies or small sample size. These results provided evidence that more RCTs of large samples are needed in the future.

The sensitivity analysis showed that the pooled results had not changed significantly when any one study was excluded based on subgroups. It meant the results in this meta-analysis were stable, no matter for the participation rate or non-participation rate. Additionally, the I^2 was reduced to 0.0% in the full-cathartic preparation CTC subgroup by excluding one of the studies in both participation and non-participation rate.²⁴ This study was a single-centric population-based RCT and was set up to reduced- and full-preparation CTC groups, respectively. One possible reason for heterogeneity was that the participation rate in the colonoscopy group is relatively low (14.8%). The Sali et al explained the lack of involvement of general practitioners and a prefixed appointment for the examination might cause the low participation rate in colonoscopy.²⁴ But Stoop et al suggested that the participation rate in all of the screening methods may be increased by involving more actively general practitioners in the invitation process.²² So, more researches are needed to confirm whether the involvement of general practitioners can influence the participation rate.

Our systematic review has several limitations. Firstly, only five studies were included. Because only a small number of published studies were collected, no absolute conclusion can be drawn. The participation rate was not with statistic significance, but in contrast, the non-participation rate reached statistic difference. Added with the cumulative meta-analysis, statistic evidence was provided that more large RCTs are needed in the future, especially on the topic of reasons for the failure of examination,

compliance with preparation requirements, and the patients' perceptions or preferences because there has not been any RCT about these topics. Additionally, the protocol of our study have not been registered on the website before conducting this work of meta-analysis, so there might be resulting in the potential for bias in this review. Finally, health insurance might be a very important factor affecting the participation rate and non-participation rate. None of the studies mentioned whether their population was reliant on health insurance. The more in-depth studies comparing costs are needed in the future.

CONCLUSION

The participation rate was higher at CTC than colonoscopy, although the difference did not reach statistical significance. But the non-participation rate was with statistical difference. Screening population seemed more likely to participate in the reduced/no cathartic preparation CTC. Statistical evidence was provided for more large RCTs are needed in the future.

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