Divergent detection rates of fecal immunochemical test and questionnaire-based risk assessment for detecting proximal and distal advanced colorectal adenomas

Hong-Da Chen, Ming Lu, Yu-Han Zhang, Min Dai

Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China.

To the Editor: Fecal immunochemical tests (FITs) are immunoassays that are designed to detect human hemoglobin to indicate the occurrence of colonic neoplasia, which have been widely used in global colorectal cancer (CRC) screening programs. Previous diagnostic studies demonstrated that strong gradient in site-specific sensitivity existed with typically higher rate for advanced adenoma located in distal colon/rectum than that in the proximal parts, which may be explained by the colonic transition time affecting the degradation of hemoglobin, and the shape of adenoma (pedunculated, flat, and sessile) in different anatomic regions.[1] In addition, questionnaire-based risk assessment (QRA) using the established CRC-related risk factors has been proposed to identify high-risk populations for CRC screening.[2] However, previous studies demonstrated that site-specific differences existed for several risk factors.[3,4] In a CRC screening setting, whether and to what extent the FIT and QRA would affect the site-specific detection rate of colorectal neoplasia have not been evaluated. Therefore, we aimed to empirically evaluate the site-specific variations of the detection rates of adenomas for the FIT- and QRA-based screening based on a population-based CRC screening trial (TARGET-C).

The study was conducted in the context of an ongoing TARGET-C trial consisted of 19,546 participants, aiming to evaluate the effectiveness of colonoscopy, FIT, and risk-adapted screening approaches in CRC screening in China, and the detailed study protocol has been previously published.[5,6] For the present study, we included 3825 subjects aged 40 to 74 years undertaking colonoscopy in the baseline screening in 2018–2019, of which 1665 were for screening purpose (colonoscopy arm), 1436 were for diagnostic purpose following positive-FIT (FIT arm or risk-adapted screening arm), and 724 were for diagnostic purpose following positive-QRA (risk-adapted screening arm). This study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences and Peking Union Medical College (No. 18-013/1615). All participants provided written informed consent.

For the QRA use in the present study, the modified Asian-Pacific colorectal screening (APCS) score was used for risk stratification, including five risk factors of CRC (age, sex, family history of CRC among first-degree relatives, smoking, and body mass index [BMI]). Each factor is allocated a score, as followed described: age (0 point: 50–54 years; 1 point: 55–65 years; 2 points: 65–74 years); sex (0 point: female; 1 point: male); family history of CRC among first-degree relatives (0 point: absent; 1 point: present); smoking (0 point: non-smoker; 1 point: current or past smoker); and BMI (0 point: <23; 1 point: ≥ 23). The cumulative score was calculated. Subjects with scores ≥ 4 were defined as high-risk and were referred for colonoscopy; those with scores <4 were defined as low-risk and were referred for FIT screening.

A self-administered qualitative FIT for hemoglobin (Pupu Tube, New Horizon Health Technology, Hangzhou, China) was used in this trial. The FIT enabled visual interpretation of the test results as positive or negative by eye if the fecal hemoglobin concentration exceeded the threshold specified by the manufacturer (100 ng Hb/mL, equivalent to 4 μg Hb/g feces). Participants with confirmed positive-FIT results were scheduled for subsequent diagnostic colonoscopy. Additional information regarding the study design is provided in the Supplementary File, http://links.lww.com/CM9/A447.

The primary outcome of interest was the detection rate for advanced adenoma or non-advanced adenoma, which was

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001346

Correspondence to: Prof. Min Dai, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China
E-Mail: daimin2002@hotmail.com

Chinese Medical Journal 2021;134(5)
Received: 11-09-2020 **Edited by:** Jing Ni

Table 1: Differences in detection rate of colorectal adenoma among subjects performing colonoscopy with different indications (*n*=3825).

Outcome	Site	Detected cases (*n*)	Detection rate (%, 95%CI)	Rate ratio	*P value*[*]	Rate difference (%, 95% CI)
Advanced adenoma						
Colonoscopy ($n=1665$)	Distal	52	3.12 (2.39–4.07)	1.24 (0.83–1.85)	Reference	0.60 (–0.52–1.73)
	Proximal	42	2.52 (1.87–3.39)	Reference		Reference
FIT ($n=1436$)	Distal	124	8.64 (7.29–10.20)	2.21 (1.63–3.00)	0.025	4.74 (2.97–6.50)
	Proximal	56	3.90 (3.01–5.03)	Reference		Reference
QRA ($n=724$)	Distal	50	6.91 (5.28–8.99)	1.47 (0.96–2.24)	0.567	2.21 (–0.20–4.62)
	Proximal	34	4.70 (3.38-6.49)	Reference		Reference
Non-advanced adenoma						
Colonoscopy ($n=1665$)	Distal	207	12.43 (10.93–14.10)	1.35 (1.11–1.64)	Reference	3.24 (1.14–5.35)
	Proximal	153	9.19 (7.89–10.67)	Reference		Reference
FIT ($n=1436$)	Distal	228	15.88 (14.08–17.86)	1.37 (1.14–1.65)	0.915	4.32 (1.81–6.83)
	Proximal	166	11.56 (10.00–13.32)	Reference		Reference
QRA ($n=724$)	Distal	105	14.50 (12.13–17.26)	1.21 (0.93–1.58)	0.514	2.49 (–1.01–5.98)
	Proximal	87	12.02 (9.85–14.59)	Reference		Reference
Any adenoma						
Colonoscopy ($n=1665$)	Distal	259	15.56 (13.89–17.38)	1.33 (1.12–1.58)	Reference	3.84 (1.52–6.17)
	Proximal	195	11.71 (10.25–13.35)	Reference		Reference
FIT ($n=1436$)	Distal	352	24.51 (22.36–26.80)	1.59 (1.37–1.85)	0.125	9.05 (6.15–11.96)
	Proximal	222	15.46 (13.68–17.42)	Reference		Reference
QRA ($n=724$)	Distal	155	21.41 (18.58–24.54)	1.28 (1.03–1.59)	0.786	4.70 (0.66–8.74)
	Proximal	121	16.71 (14.17–19.60)	Reference		Reference

FIT: Fecal immunochemical test; QRA: Questionnaire-based risk assessment. [*] *P* values were calculated comparing the differences of rate ratios between the examined group and the colonoscopy group using the *Z*-test proposed by Douglas G Altman and J Matrtin Bland (BMJ 2003;326: 219).

calculated by numbers of the carriers with disease divided by the total number included participants. Advanced adenoma was defined as high-grade dysplasia, villous or tubular-villous histologic features, measuring 1 cm or more in diameter. Regarding the location of the neoplasm, the proximal colon was considered to include the splenic flexure and all segments proximal to it, and the rest was considered distal colon/rectum. For subjects having multiple adenomas, the outcome and anatomic location were defined according to the most advanced one. Site-specific detection rate was therefore calculated and compared between the three groups of subjects undertaking colonoscopy, that is, screening purpose, diagnostic purpose either of positive-FIT or positive-QRA.

For the 3825 included subjects, the mean (standard deviation) age was 60.5 (6.3) years and slightly more men ($n=1977$, 51.7%) were included. Overall, among the subjects undertaking screening colonoscopy and diagnostic colonoscopy after positive-FIT, no significant differences regarding the distribution of sociodemographic factors were observed. For subjects undertaking diagnostic colonoscopy after positive-QRA, the distribution of these factors was significantly different than the other two groups, because factors of age, sex, BMI, cigarette smoking, and history of CRC among the first-degree relatives were included in the risk assessment [Supplementary Table 1, http://links.lww.com/CM9/A447].

For subjects undertaking screening colonoscopy, the detection rates of advanced adenoma located in the distal colon/rectum and proximal colon were 3.12% (95% CI: 2.39–4.07%) and 2.52% (95% CI: 1.87–3.39%), the rate ratio $_{\text{distal } vs. \text{ proximal}}$ was 1.24 (95% CI: 0.83–1.85), and the rate difference $_{\text{distal } vs. \text{ proximal}}$ was 0.60% (95% CI: −0.52 to 1.73%). As expected, the detection rates of advanced adenoma increased for subjects with either positive-FIT (proximal *vs.* distal: 8.64% [95% CI: 7.29–10.20%] *vs.* 3.90% [95% CI: 3.01–5.03%]) or positive-QRA (proximal *vs.* distal: 6.91% [95% CI: 5.28–8.99%] *vs.* 4.70% [95% CI: 3.38–6.49%]), however, the rate ratio$_{\text{distal } vs. \text{ proximal}}$ increased to 2.21 (95% CI: 1.63–3.00; $P_{\text{FIT } vs. \text{ colonoscopy}} = 0.025$) and 1.47 (0.96–2.24; $P_{\text{QRA } vs. \text{ colonoscopy}} = 0.567$), respectively; and the rate difference$_{\text{distal } vs. \text{ proximal}}$ increased to 4.74% and 2.21%, respectively. Regarding detection for non-advanced adenoma and any adenoma, there were no significant differences in detection rates among the subjects of either positive-FIT or positive-QRA compared with the subjects undertaking screening colonoscopy. Detailed results are shown in Table 1.

In this retrospective analysis based on a population-based CRC screening trial, by setting the yield of screening colonoscopy as a reference reflecting the real-world prevalence of adenoma in different anatomic locations, we found that FIT- and QRA-based screening had large variations in terms of detection rates for proximal and distal located advanced adenoma, although the difference was only statistically significant for the FIT-based approach.

There were several reasons that might explain the variations of the detection rates for advanced neoplasia located in the proximal and distal colon/rectum. First, most of the distal adenomas are pedunculated, which may therefore be more prone to be bleeding than the flat and

sessile adenomas that are more likely to be detected in the proximal colon. Second, the degradation time for fecal hemoglobin is longer for proximal lesions than distal ones, which may therefore lead to the variation of the detection rate, although data to support this are sparse.

Previous studies have suggested that lowering the positivity threshold of FIT may help to increase the sensitivity for detecting proximal neoplasm. The positivity threshold of FIT used in the present study was 4 μg Hb/g feces, which was lower than other FIT-based CRC screening programs.[8] Based on our results, such a strategy of lowering the positivity threshold of FIT may not aid such an issue. Another important finding of our study was that QRA also lead to divergent detection rates for proximal and distal neoplasms, although the differences were not statistically significant. Although the reasons behind this cannot be fully understood, we inferred that a series of factors such as smoking and BMI had different magnitudes of attributable risk in proximal and distal CRC, as demonstrated in a recently published study.[3,4] Further attention should be paid to this issue, since combining environmental and polygenic factors has been suggested in tailored risk-adapted CRC screening.

Our study has limitations. First, the analysis was derived from a single round of screening, however, the current finding indicated that the differences between the detection rate for proximal and distal advanced adenoma may be even larger over multiple rounds of screening. Second, despite the overall large sample size of the trial, numbers of the advanced adenomas were still rather limited leading to rather wide confidence intervals, which should be addressed in further larger studies.[7]

To sum up, we empirically demonstrated the divergent detection rates of proximal and distal advanced adenomas existed in FIT-based but not in the QRA-based CRC screening. Further efforts should be made to optimize the effectiveness of CRC screening by improving the lower detection rate of proximal advanced adenomas.

Funding

This work was supported by grants from the CAMS Innovation Fund for Medical Sciences (No. 2017-I2M-1-006), the National Natural Science Foundation of China (No. 81703309), Beijing Nova Program of Science and Technology (No. Z191100001119065), and the Natural Science Foundation of Beijing Municipality (No. 7202169).

Conflicts of interest

None.

References

1. Lu M, Luo X, Li N, Chen H, Dai M. Diagnostic accuracy of fecal occult blood tests for detecting proximal versus distal colorectal neoplasia: A systematic review and meta-analysis. Clin Epidemiol 2019;11:943–954. doi: 10.2147/CLEP.S213677.
2. Peng L, Weigl K, Boakye D, Brenner H. Risk scores for predicting advanced colorectal neoplasia in the average-risk population: A systematic review and meta-analysis. Am J Gastroenterol 2018;113:1788–1800. doi: 10.1038/s41395-018-0209-2.
3. Wang L, Lo CH, He X, Hang D, Wang M, Wu K, *et al*. Risk factor profiles differ for cancers of different regions of the colorectum. Gastroenterology 2020;159:241–256. e13. doi: 10.1053/j.gastro.2020.03.054.
4. Wei EK, Colditz GA, Giovannucci EL, Wu K, Glynn RJ, Fuchs CS, *et al*. A comprehensive model of colorectal cancer by risk factor status and subsite using data from the nurses' health study. Am J Epidemiol 2017;185:224–237. doi: 10.1093/aje/kww183.
5. Chen H, Li N, Shi J, Ren J, Liu C, Zhang Y, *et al*. Comparative evaluation of novel screening strategies for colorectal cancer screening in China (TARGET-C): A study protocol for a multicentre randomised controlled trial. BMJ Open 2019;9:e025935. doi: 10.1136/bmjopen-2018-025935.
6. Chen H, Lu M, Liu C, Zou S, Du L, Liao X, *et al*. Comparative evaluation of participation and diagnostic yield of colonoscopy vs. fecal immunochemical test vs. risk-adapted screening in colorectal cancer screening: Interim analysis of a multicenter randomized controlled trial (TARGET-C). Am J Gastroenterol 2020;115:1264–1274. doi: 10.14309/ajg.0000000000000624.
7. Brenner H, Niedermaier T, Chen H. Strong subsite-specific variation in detecting advanced adenomas by fecal immunochemical testing for hemoglobin. Int J Cancer 2017;140:2015–2022. doi: 10.1002/ijc.30629.
8. Selby K, Levine EH, Doan C, Gies A, Brenner H, Quesenberry C, *et al*. Effect of sex, age, and positivity threshold on fecal immunochemical test accuracy: A systematic review and meta-analysis. Gastroenterology 2019;157:1494–1505. doi: 10.1053/j.gastro.2019.08.023.

How to cite this article: Chen HD, Lu M, Zhang YH, Dai M. Divergent detection rates of Fecal immunochemical test and questionnaire-based risk assessment for detecting proximal and distal advanced adenomas. Chin Med J 2021;134:605–607. doi: 10.1097/CM9.0000000000001346