RESEARCH ARTICLE

Accuracy of Self-Checked Fecal Occult Blood Testing for Colorectal Cancer in Thai Patients

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Abstract

Purpose: Colorectal cancer (CRC) screening with fecal occult blood testing (FOBT) has been associated with a reduction in CRC incidence and CRC-related mortality. However, a conventional FOBT requires stool collection and handling, which may be inconvenient for participants. The EZ-Detect™ (Siam Pharmaceutical Thailand) is a FDA-approved chromogen-substrate based FOBT which is basically a self-checked FOBT (no stool handling required). This study aimed to evaluate the accuracy of EZ-Detect for CRC detection. Methods: This prospective study was conducted in the Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand between November 2013 and May 2014. Some 96 patients with histologically-proven CRC and 101 patients with normal colonoscopic findings were invited to perform self-checked FOBT according to the manufacturer's instructions. Results were compared with endoscopic and pathologic findings. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for CRC detection were calculated. Results: The present study revealed the sensitivity, specificity, PPV and NPV of this self-checked FOBT for CRC detection to be 41% (95% CI: 31-51), 97% (95% CI: 92-99), 93% (95% CI: 81-98) and 63% (95% CI: 55-70), respectively. The overall accuracy of the self-checked FOBT for identifying CRC was 70%. The sensitivity for CRC detection based on 7th AJCC staging was 29% for stage I, 32% for stage II and 50% for stage III/IV (P=0.19). The sensitivity was 33% for proximal colon and 42% for distal colon and rectal cancer (P=0.76). Notably, none of nine infiltrative lesions gave a positive FOBT. Conclusions: The self-checked FOBT had an acceptable accuracy of CRC detection except for infiltrative tumors. This home-administrated or 'DIY' do-it-yourself FOBT could be considered as one non-invasive and convenient tool for CRC screening.

Keywords: Colorectal cancer - screening - fecal occult blood testing - self-checked - Thailand

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Introduction

Colorectal cancer (CRC) is the leading cause of cancer death worldwide including the Asia-Pacific region. The incidence of CRC has been increasing up to 15-20% in the last decade in some Asian countries (Mosli and Al-Ahwal, 2012). In Thailand, CRC is currently the third most commonly diagnosed cancer (Khuhaprema and Srivatanakul, 2008). In order to reduce CRC-related mortality, prevention, early detection and proper management must be implied. There is strong evidence that screening program decreases the incidence and mortality of CRC (Hewitson et al., 2007). Among various screening tools, fecal occult blood testing (FOBT) has been widely and effectively used in several population-based CRC screening programs (Katicic et al., 2012; Logan et al., 2012; Zavoral et al., 2014). According to a survey of Thai general surgeons, FOBT was the most popular modality of CRC screening (Lohsiriwat et al., 2009). In a recent community-based survey in the United States, a large proportion of respondents preferred FOBT over colonoscopy for CRC screening (DeBourcy et al., 2008).

Despite the popularity, proven efficacy and cost-effectiveness of FOBT-based screening program (Hewitson et al., 2007; Lansdorp-Vogelaar et al., 2011), there are several barriers for participants to apply FOBT for CRC screening. These barriers included a lack of knowledge and limited access to FOBT kit (Norwati et al., 2014), a long waiting time for analysis (Brouse et al., 2003) and, more interestingly, the unpleasantness of the stool collection procedure (Hynam et al., 1995; Lowenfels, 2002; Jones et al., 2010). As a result, the method of specimen collection and analysis could have a significant influence on patient's enrollment and good compliance with FOBT.

A FOBT without a need of stool handling is currently available including the EZ-Detect™ (Biomerica USA/ Siam Pharmaceutical Thailand). The EZ-Detect is a chromogen-substrate based FOBT. It is a FDA-approved

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FOBT kit which is basically a self-checked FOBT without any stool handling required. However, there are very limited published data of this self-checked FOBT (Tate et al., 1989; Hou and Chen, 2004; Cruz-Correa et al., 2007), and no study examining the accuracy of such a FOBT kit in Thailand has been published.

The primary objective of the present study was therefore to determine the sensitivity, specificity, positive predictive value, and negative predictive value of EZ-Detect (a self-checked FOBT) for CRC detection. The secondary objective was to compare the results of EZ-Detect with pathologic findings and tumor staging.

Materials and Methods

After obtaining approval from the Institutional Review Board (SIRB 604/2556), patients with histologically proven adenocarcinoma of the colon and rectum being scheduled for elective tumor resection were enrolled. Individuals with normal colonoscopic findings were also included in the study as control cases. Written informed consent was obtained from each subject. Patients with CRC were excluded from the present study for one of the following reasons: age <18 years, time interval between colonoscopic biopsy and FOBT testing <2 weeks, neoadjuvant treatment, active or gross hematochezia, menstruation, administration of anticoagulant/aspirin or non-steroidal anti-inflammatory drugs, and unresectable primary cancer. Distant metastasis was not an exclusion criterion because this study focused primarily on CRC detection.

According to the manufacturer's instruction, each subject was asked to perform self-checked FOBT (EZ-Detect™; Siam Pharmaceutical Thailand) for 3 consecutive bowel openings. The package of EZ-Detect consists of 5 biodegradable papers coated with tetramethylbenzidine (TMB), a chromogenic dye. After the stool was in the toilet bowl, one piece of the papers was placed into the bowl. If a significant amount of blood in stool presented (at least 2 mg hemoglobin/100 mL water), TMB-coated paper would be oxidized by oxygen molecules deliberated from hemoglobin. As a result, oxidized TMB turned from colorless to blue-green color, which was spotted as a big cross in the middle of the paper within 2 minutes. Of note, any blue-green color spotted in the central area of the paper was also considered as a positive test (Figure 1). After use, this testing paper was simply flushed into the toilet bowl. The unused papers were kept in a sealed envelope. A positive result on any of 3 testing papers was determined as 'positive' EZ-Detect. Consequently, subjects would be categorized as 'positive' or 'negative' EZ-Detect. Notably, subjects were excluded if they cannot complete the 3-time testing.

All specimens resected from CRC patients were sent for pathologic examination. Proximal cancer was defined as a tumor located proximal to the splenic flexure. Distal cancer was defined as a tumor at or distal to the splenic flexure. Tumor staging was classified based on the seventh edition of the American Joint Committee for Cancer (AJCC) staging for colorectal cancer. Results of FOBT

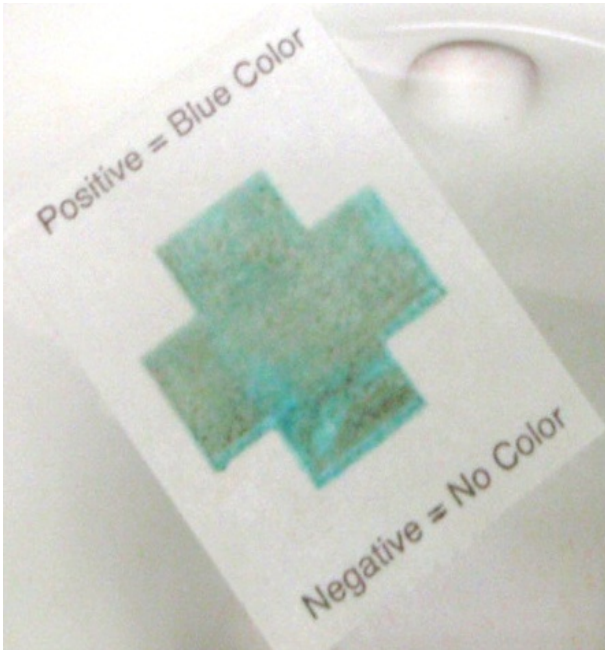

Figure 1. 'Positive' Self-Checked FOBT (EZ-Detect); a change from colorless to blue-green color spotted in the central area of a testing paper as a big cross

were compared with endoscopic and pathologic findings. Sensitivity, specificity, positive predictive value, and negative predictive value of this self-checked FOBT were analyzed with 95% Confidence Interval (95% CI) Analysis for Windows (Statistics with Confidence, 2nd Edition, BMJ Books, London 2000). The Pearson Chi-square test and Fisher's exact test were used for categorical data. A P-value of less than 0.05 was considered statistically significant.

Results

This study included 96 CRC patients and 101 individuals with normal colonoscopic findings. In the CRC group, there were 58 male (60%) with an average age of 65 years (range 33-93) and an average tumor size of 5 cm (range 0.8-12). In the control group, there were 53 male (52%) with an average age of 63 years (range 31-84). The self-checked FOBT was positive in 39 cases of the CRC patients (41%), and in 3 cases of the control subjects (3%).

The sensitivity, specificity, PPV, and NPV of this self-checked FOBT for CRC detection were 41% (95% CI: 31-51), 97% (95% CI: 92-99), 93% (95% CI: 81-98) and 63% (95% CI: 55-70), respectively. The overall accuracy of EZ-Detect for identifying invasive CRC was 70%. The sensitivity for CRC detection based on 7th AJCC staging was 29% for stage I CRC (n=21), 32% for stage II CRC (n=25) and 50% for stage III/IV CRC (n=50); p=0.19. Test sensitivity for proximal colon cancer (n=12) was slightly inferior to that for distal colorectal cancer (n=84), but it did not reach statistical significance (33% vs 42%; p=0.76). According to tumor morphology, none of 9 infiltrative tumors had positive FOBT whereas 39 out of 87 non-infiltrative lesions (45%) had positive FOBT (p=0.10).

Discussion

This study demonstrated that a self-checked FOBT (EZ-Detect) had a sensitivity of 41%, a specificity of 97% and an overall accuracy of 70% for invasive CRC detection. The sensitivity of this self-checked FOBT was slightly higher for distal tumor and tumor with advanced staging. Notably, it was insensitive to detect an infiltrative-type CRC. Interestingly, the overall accuracy of the FOBT kit in the present study was well comparable to that reported in a previous study (Tate et al., 1989), in which the EZ-Detect had 36% sensitivity, 89% specificity and 16% PPV for CRC detection.

An in vitro study showed that the EZ-Detect was sensitive to the same degree of blood that could react to the Haemoccult, a widely used guaiac-based FOBT (Tate et al., 1989). However, clinical studies revealed a better sensitivity of Haemoccult for identifying advanced adenoma (Cruz-Correa et al., 2007) and invasive CRC (Tate et al., 1989). It is possible that the amount of fecal blood might be insufficient to effectively activate the EZ-Detect test which requires at least 2 mg hemoglobin per 100 mL of water (according to the manufacturer's instruction). For example, despite a significant amount of blood within stool, a small volume of stool in a relative large bowl of lavatory could result in a negative test for EZ-Detect. In contrast, with conventional FOBT there is direct application of stool to testing papers thus avoiding the problem of specimen dilution and practically resulting in a positive test.

A higher sensitivity of FOBT for distal colon cancer and rectal cancer compared with proximal colon cancer in the present study was in accordance with that reported in a recent systematic review of FOBT sensitivity (Haug et al., 2011), a nationwide CRC screening program in Korea (Shin et al., 2013), and a previous study from Thailand (Lohsiriwat et al., 2007). The higher FOBT sensitivity for distal CRC could be possibly explained by some reasons such as a higher level of fecal hemoglobin in those with distal CRC (Park et al., 2010), and the degradation of hemogloblin originated from proximal colon (Haug et al., 2011). More specifically, since the reaction of this self-checked FOBT depends on the oxidative effect of oxygen molecules deliberated from hemoglobin, it is possible that occult blood on the surface of stool from distal colon cancer and rectal cancer was more prominent than those mixed in the stool from right-sided cancer. Consequently, FOBT in distal CRC could be more reactive than that in proximal colon cancer.

The present study also revealed a better sensitivity of this self-checked FOBT for more advanced stage CRC. This finding was similar to that reported from other studies of FOBT (Tibble et al., 2001; Lohsiriwat et al., 2007). It is possible that an advanced CRC is more likely to be ulcerated and bled. Meanwhile, tumor morphology could have a great impact on the sensitivity of FOBT for CRC detection. For example, the present study showed that FOBT was negative for all of 9 infiltrative tumors. Meanwhile, several authors reported a lower sensitivity of FOBT for small neoplasms (Tibble et al., 2001; Strul & Arber, 2002; Nakazato et al., 2006).

Although some conventional FOBT kits might have a higher sensitivity for CRC detection than this self-checked FOBT (Tate et al., 1989; Cruz-Correa et al., 2007), the self-checked FOBT has some advantages. Firstly and clearly, it is very convenient and needs no stool handling. Individuals can see the results themselves, immediately at home, thus reducing time and cost to attend a healthcare service. Another possible advantage of this self-checked FOBT is that the chromogen-substrate system does not require vigorous dietary restriction because the EZ-Detect is designed to detect blood from the alimentary system, which is mainly coated on the surface of stool and deliberate oxygen molecules to activate chemicals impinged on a testing paper. Other sources of blood and peroxidase, such as raw meat and some vegetables which are usually imbedded within the stool or denatured in the digestive system, do not affect the process (Cruz-Correa et al., 2007). As a result, several studies frequently reported that a large proportion of individuals preferred this self-checked FOBT to a conventional FOBT (Tate et al., 1989; Hou and Chen, 2004; Cruz-Correa et al., 2007). Interestingly, Hou and Chen reported that Chinese participants had a higher rate of perceived acceptance and screening completion for a self-checked FOBT than a conventional FOBT. Moreover, intention towards a self-checked FOBT significantly increased in the coming year (Hou and Chen, 2004). Indeed, some improvement of diagnostic accuracy of self-checked FOBT is required. Also, annual testing of FOBT is highly recommended due to a significant improvement of CRC detection over time (Rex et al., 2009; Halloran et al., 2012).

Some limitations of this study should be addressed. Firstly, it had a relatively small number of participants with a selective group of patients, which certainly did not represent a general population-especially for patients with proximal CRC. Larger studies of self-checked FOBT are definitely required. Secondly, the present study did not neither compare the results with a conventional FOBT nor check the accuracy of participant's interpretation. It was evident that some participants may not notice some spotting color change in the central part of testing paper, or ones were unable to detect any color change of the test, especially those with color-blindness (Tate et al., 1989).

In summary, the present study demonstrated the sensitivity, specificity, and overall accuracy of EZ-Detect (a self-checked FOBT) for detecting invasive CRC were 41%, 97% and 70%, respectively. This do-it-yourself (DIY) or home-administrated FOBT could be an alternative to a conventional FOBT for CRC screening because of its convenience and no requirement for stool collection. Finally, a self-checked FOBT would potentially be used as a non-invasive tool to promote and to improve the compliance of CRC screening scheme.

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