Colorectal Cancer Screening: Is there a Role for Stool DNA Testing?

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Abstract

Colorectal cancer (CRC) is a major cause of morbidity and mortality throughout the world, being the third most common cancer in the world and the fourth most common cause of death. In recent years increased rates of CRC incidence has been reported in developing countries. The presence or absence of screening programs is an important factor in determining overall changes of CRC epidemiology. CCR screening modalities vary throughout the world, and the differences are probably due to the cost and availability of diagnostic resources. Colonoscopy, sigmoidoscopy, and FOBTs are all recommended screening tests, but adherence rates are low. Additional stool-based methods that offer more options for CRC have been developed, including fecal DNA tests. Stool-based DNA testing is noninvasive, and it is more sensitive and specific than FOBTs, only a single stool sample is needed, the test does not require diet or medication restrictions, and it evaluates the whole colon and rectum. The disadvantages of stool-based DNA testing include: high cost, lower sensitivity comparing with colonoscopy, and the fact that if the stool-based test is positive, colonoscopy needs to be done anyway. Finally, relatively high rates of false-positive and false-negative results limit the accuracy of these tests, thereby restricting their widespread use.

Keywords: Colorectal cancer; Screening; Stool DNA testing

Mini Review

Colorectal cancer (CRC) is a major cause of morbidity and mortality throughout the world, being the third most common cancer in the world and the fourth most common cause of death, with nearly 1.4 million new cases diagnosed in 2012 [1,2].

CRC affects men and women almost equally and it accounts for over 9% of all cancer incidence, but the incidence significantly varies [1,3].

It is predicted that worldwide the number of cases will rise to 1.36 million for men and 1.08 million for women by 2035. In 2012 there were about 746,000 cases diagnosed in men and 614,000 cases in women. Approximately 2.4 million cases of colorectal cancer will be diagnosed annually worldwide by 2035 [2].

In recent years increased rates of CRC incidence has been reported in developing countries, countries which previously showed a decreased risk of CRC [1].

Although, in many regions of the world, data regarding risk factors for CRC are limited, increased rates of CRC incidence reported in developing countries in economic transition, and in other countries of Eastern Europe, are likely the result of increasing prevalence of obesity associated with a western-type lifestyle, including increased consumption of high calorie foods, and physical inactivity [4-7]. In addition, the high prevalence of smoking, reported by increased rates of lung cancer mortality (which in developing countries have exceeded the mortality rates from developed countries, such as the U.S.) [3], may play an important role in the increased incidence of CRC in developing countries.

The presence or absence of screening programs is an important factor in determining overall changes of CRC epidemiology, because screening increases short term incidence of CRC, by increasing CRC diagnosis, and reduces long-term incidence of CRC by premalignant lesions treatment [8]. For this reason, CRC screening programs decreases mortality, by decreasing the incidence and by increasing the diagnosis of early-stage curable tumors [9-11]. In fact, the increased use of screening has been cited as one of the most important factors responsible for the recent decline in incidence and mortality rates of CRC in the U.S. [12,13].

CCR screening modalities vary throughout the world, and the differences are probably due to the cost and availability of diagnostic resources, which directly influences the design of screening programs. Although colonoscopy can be considered as the gold standard for CRC screening, it requires a well-trained examiner, additional costs, and is less convenient for the patient [14]. Therefore, CRC screening based on colonoscopy is less feasible in most countries, and not practical in almost all countries with limited resources. Consequently, although less sensitive than structural examinations, fecal occult-blood testing (FOBT) is a cheap and easy method, and is a feasible option for CRC screening in many countries.

The U.S. current recommendations for screening and diagnosis of adenomatous polyps and CRC in average risk adults ( > 50 years) include either annual fecal testing with guaiac tests (gFOBT) or immunochemical-based tests (iFOBT), stool DNA test with high sensitivity, flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, double-contrast barium every 5 years, or CT colonography every 5 years [13].

Structural examinations are invasive procedures that require prior preparation of the colon, and are associated with various levels of risk [10]. Therefore if the resources are not available, or patients refuse these diagnostic procedures, annual fecal occult blood test (FOBT) is recommended, including gFOBT and iFOBT. gFOBT, which is one of the most used tests, was associated with an up to 33% decrease in CRC mortality [15], but is less sensitive than structural examinations, and
less effective in preventing CRC, as sensitivity in the diagnosis of premalignant lesions is decreased [13].

Colonoscopy, sigmoidoscopy, and FOBTs are all recommended screening tests, but adherence rates are low (44.6% for FOBTs, 47.3% for sigmoidoscopy/colonoscopy) [16]. Studies showed that nearly a third of the patients will refuse any form of invasive testing, but are willing to undergo noninvasive testing [16,17].

Additional stool-based methods that offer more options for CRC have been developed, including fecal DNA tests [18]. Stool DNA testing detects the presence of known DNA alterations during colorectal carcinogenesis in tumor cells shed into stool [19]. Because DNA changes may differ between colon cancers, stool DNA tests typically target multiple markers in order to achieve high detection rates. Also, because DNA markers may be present in only small quantities in stool, very sensitive laboratory methods are required. Stool DNA testing has been shown to be more effective than FOBTs at detecting CRC and precancerous polyps. The new stool DNA tests demonstrate high detection rates of early-stage CRC (52-91% sensitivity, and 93-97% specificity) [20], but no clinical trials have evaluated the impact of fecal DNA testing on patient management or CRC-related mortality. Also, there is no published evidence regarding the appropriate interval between screening stool DNA tests, although a 5-year interval is currently recommended [20].

Stool-based DNA testing is noninvasive, and it is more sensitive and specific than FOBTs, only a single stool sample is needed, the test does not require diet or medication restrictions, and it evaluates the whole colon and rectum [17,21].

The disadvantages of stool-based DNA testing include: high cost ($400-800), lower sensitivity comparing with colonoscopy, and the fact that if the stool-based test is positive, colonoscopy needs to be done anyway. Finally, relatively high rates of false-positive and false-negative results limit the accuracy of these tests, thereby restricting their widespread use [17,21].

A recent study [22] evaluated the performance characteristics of a multitarget stool DNA (molecular assays for aberrantly methylated BMP3 and NDRG4 promoter regions, mutant KRAS, β-actin, and an immunochromatography assay for human hemoglobin) in the detection of CRC. The secondary aims of the study were to determine the performance of the DNA test in the detection of advanced precancerous lesions and to compare it with a commercially available fecal immunochemical test (FIT) for human hemoglobin in the detection of both CRC and advanced precancerous lesions. The sensitivity of the DNA test for the detection of both CRC and advanced precancerous lesions exceeded that of FIT by an absolute difference of nearly 20%, but FIT was more specific for the detection of both CRC and advanced precancerous lesions. The conclusion of the study was that a stool test combining altered human DNA and fetal hemoglobin showed higher single-application sensitivity than a commercial FIT for both CRC and advanced precancerous lesions, although with lower specificity [22].

Results of clinical trials indicate that fecal DNA testing can detect precancerous and cancerous colorectal lesions with moderate to high accuracy, especially when multiple mutations and DNA abnormalities are assessed. However, the evidence is too limited to fully evaluate diagnostic performance and, to date, as we already mentioned, no clinical trials have evaluated the impact of fecal DNA testing on patient management or CRC-related mortality [20,23].

NCCN guidelines stipulates that for patients unwilling or unable to have screening colonoscopy, there is increasing evidence that a stool DNA test may provide a valuable noninvasive option, but more research is necessary to determine the optimal testing interval. Only one stool DNA test, ColoSureTM, is currently available in U.S., however, stool DNA testing has not yet been approved by the FDA, and is currently not considered a first-line screening tool [19].

In conclusion, although fecal DNA testing is commercially available, it is not yet ready for prime time. An important fact to remember is that the majority of Americans are never screened for CRC despite long-standing, although imperfect, screening methods, due to the fact that there is no universal medical record system to allow better tracking of patient care, and there is no sufficient public education programs to encourage patients to utilize preventive care services, and thus to benefit from early cancer diagnosis. These issues are the true challenges that are currently faced in eradicating CRC [24].

Detection of precancerous and early-stage CRC is central to improving patient prognosis. Recommendations, guideline’s and CRC screening programs vary widely around the world. Most countries have national screening programs using FOBTs, although few countries (Poland and Germany) [25] are using colonoscopy. However, most screening programs are not national and many countries in North America and Europe are performing screening pilot programs intended to assess the potential for screening implementation [26-28]. These pilot studies are using a variety of screening assays, alone or in combination (FOBTs, colonoscopy, and flexible sigmoidoscopy).

Because CRC mortality rates are increasing in developing countries, especially in those in transition, who have adopted a western-type lifestyle, or have aging populations, it is likely that implementation of CRC screening strategies will become a priority.

References