Fecal occult blood test for colorectal cancer screening

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Introduction

Colorectal cancer (CRC) is a major health concern and a leading cause of cancer death in the Western world. The estimated lifetime risk of CRC is 5% to 6%, the incidence rate increases sharply after the age of 50. Approximately 75% of new cases occur in individuals at average risk [1, 2]. Worldwide, it is estimated that there will be over one million new CRC cases in the year 2001 (personal communication), and the annual age-adjusted incidence rate is 57 per 100,000. Survival is directly related to the extent of disease at the time of diagnosis. Those diagnosed at an advanced stage have an estimated 5-year survival rate of 7%, in contrast with a survival rate of 92% for individuals detected at an early stage, since advanced CRC is largely refractory to conventional therapy and is one of the least curable malignancies [3].

Despite continuing advances in diagnosis and therapy, long-term survival has not improved significantly over the last four decades, and almost 50% of CRC patients will eventually die of their disease [1, 2]. This situation mandates improvement in the early detection of this surgically curable disease and preventative interventions to reduce the incidence of the disease and its downstream morbidities and mortality. Indeed, given our understanding of the pathogenesis of CRC, current screening technologies, and effective preventative interventions, CRC should be highly preventable.

Colorectal cancer has become an important issue for physicians and the general population in the last decade, ever since preventative medicine became a key issue in health care. Indeed, CRC is preventable in up to 90% of cases [4, 5]. CRC fulfils the criteria a disease must have for mass screening. Indeed, intestinal tumorigenesis is exceptionally suited for screening, since the adenoma–carcinoma sequence allows the detection and removal of pre-malignant lesions, and it is well established that patients who are maintained free of adenomas by endoscopic polypectomy are generally kept cancer free [4, 6, 7].

A study using Markov chain analysis has found that CRC decreases the life expectancy calculated for the entire US population by 292 days at age 50–54 years and by 70 days at age 70–74 years [8]. At the same time, an important controversial issue is the optimal screening approach for the average-risk population at the age of 50 years. Endoscopic screening is undoubtedly the most effective screening method, but its potential disadvantages, such as invasiveness and cost, should be considered. The simplest and most evaluated screening method available for CRC is the fecal occult blood test (FOBT). This periodic stool testing is considered a low-priced, non-invasive test that requires no cathartic preparation. It can be performed on mailed specimens without a health center visit, and may reflect the full length of the colon. On the other hand, it is a less sensitive method, since many cancers and the large majority of pre-malignant adenomas do not bleed and are therefore missed. Furthermore, high false-positive rates, due to dietary peroxidases and meat, or frequent and trivial sources of occult bleeding, lead to unnecessary colonoscopies that drive up programmatic costs.

The first national screening program with FOBT was introduced in 1977 in Germany. The evaluation of this program was limited because of confidentiality problems. Case–control studies have yielded conflicting results regarding the effectiveness of FOBT as a screening modality [9].

The rationale for the use of FOBT screening programs is based on three major long-term randomized trials. Overall, those trials using annual FOBT have reported a 15% to 33% reduction in CRC related death (for review, see reference 10). The Minnesota prospective case–controlled study [11] is the study that is most cited. It included 46,000 subjects and showed a reduction in CRC mortality, after 13–18 years of follow-up, of 33% for annual FOBT examination. Biennial testing resulted in only a minor non-significant mortality reduction (6%) after 13 years. It increased to a cumulative 21% reduction after 18 years [11, 12]. The benefit of FOBT alone in the Minnesota study was questioned, since 38% of the participants underwent colonoscopy, which may have influenced the mortality reduction rate. The authors have attributed 6% to 11% of the mortality reduction to the chance detection of lesions (especially small adenomas) by colonoscopy. Two
other large randomized trials from the UK [13] and Denmark
[14] have reported 15% to 18% decreases in mortality for
biennial FOBT after 8–10 years. As in the Minnesota study,
patients with positive results underwent colonoscopy; there-
fore, a similar debate regarding the incidental endoscopic
detection of neoplasia was raised. Some better conducted pro-
spective as well as case–control studies further support the
efficacy of FOBT screening [13–16].

Recently, Lieberman and Weiss [17] reported on their
intriguing results assessing the sensitivity of one-time screen-
ing with FOBT, sigmoidoscopy and colonoscopy in 2885
asymptomatic subjects age 50–75 years. All participants under-
went a complete colonoscopy after returning three specimens
for FOBT. Sigmoidoscopy was defined as examination of the
rectum and sigmoid during colonoscopy. A positive FOBT
was found in 23.9% of patients with advanced neoplasia
(determined as an adenoma 10 mm or larger, villous adenoma,
high grade dysplasia or carcinoma). Sigmoidoscopy alone or
combined with FOBT failed to identify 30% and 24% of
advanced neoplasia, respectively. The overall sensitivity of
FOBT for any neoplasia was 11.7%.

Towler et al. [18] performed a systematic review of the liter-
ature and found that 1000 people would have to be screened
for ~10 years in order to prevent one death from CRC.

Our review will present and discuss the pros and cons of
FOBT as a screening tool for CRC.

Rationale of the test

The FOBT exploits the tendency of CRC and large polyps to
bleed. Ideally, the subject uses a wooden stick to sample from
two areas of a formed non-bloody stool, smearing the samples
onto two windows on the test card; this procedure is repeated
for two more bowel movements. The cards are then developed
in a physician’s office or a clinical laboratory. If any of the six
windows on the three cards is positive, then the test is inter-
preted as positive, and subjects undergo evaluation of the
entire colon [19]. It is important to emphasize that a single
occult blood examination has no clinical significance in the
screening of CRC. The detection rate of adenomas and carci-
nomas by one spot FOBT screening examination is 2/1000 and
0.7/1000 screens, respectively [20].

FOBT screening offers no benefit without appropriate
follow-up diagnostic testing and treatment. It is an indirect
screening test that identifies a subgroup of the average-risk,
asymptomatic population sufficiently likely to have a clinic-
ally important CRC to justify more expensive, invasive diag-
nostic tests (e.g. colonoscopy). The screening test by itself
neither rules in nor rules out colonic neoplasia [21].

Sensitivity, specificity and positive predictive value

Usually FOBT is based on the detection of peroxidase activity
in the stool. Hemoccult II (Beckman Coulter Diagnostic,
Palo Alto, CA, USA), the most popular test kit, employs
guaiac-impregnated paper and developing solutions to detect
the oxidative conversion of a colorless compound to a colored
one in the presence of hemoglobin pseudoperoxidase activity.
Hemoccult sensa improved the sensitivity of the test; it can
detect increased peroxidase activity in the presence of smaller
amounts of fecal blood [22, 23]. On the other hand, it reduced
the specificity of the test because of an increased false-
positive ratio [22–24].

More sensitive assays are the immunochemical tests Hem-
Select (HS) and FlexSure (FS). These tests detect directly
human hemoglobin in the stool by using anti-human hemog-
lobin antibodies [23]. In the HS test, agglutination of chicken
erthrocytes coated with antibodies occurs in the presence of
intact human hemoglobin. The FS test employs the binding of
human hemoglobin to antibodies immobilized on a test strip.
A color change appears when the antibody–hemoglobin com-
plex migrates chromatographically along the strip [10, 25].

In comparative screening with guaiac and immuno-
histochemical tests, the sensitivity for CRC or large adenoma is
~50%. The best results for carcinoma detection were achieved
by a combination of the two methods, with a sensitivity of
66% and a specificity of 97% [10]. In one Japanese study,
using a 3-day FOBT, the sensitivity and specificity for the
detection of adenomas (≥1 cm), in a set of five different
immunochemical tests were 48% and 96%, respectively [26].
The positive predictive value of FOBT is ~10%; it is negative
in about half of patients with CRC [19]. Positive unhydrated
FOBT has been associated with a 22% to 58% CRC detection
rate [11–14, 27].

Lieberman et al. [28] detected polyps (1 cm or larger) in
17% of average-risk patients referred for colonoscopy with a
positive FOBT. The same author [17] recently assessed the
sensitivity of one-time screening with FOBT, sigmoidoscopy
and colonoscopy in asymptomatic subjects, aged 50–75 years.
A total of 2885 participants underwent a complete colon-
oscopy after returning three specimens for FOBT. Sigmoid-
oscopy was defined as recto-sigmoid examination during
colonoscopy. A positive FOBT was found in 23.9% of
patients with advanced neoplasia (determined as an adenoma
10 mm or larger, villous adenoma, high grade dysplasia or
carcinoma). Sigmoidoscopy alone or combined with FOBT
failed to identify 30% and 24% of advanced neoplasia, respect-
ively. The overall sensitivity of FOBT for any neoplasia
decreased to 11.7%. Other authors have reported 7% to 12%
detection rates for large adenomas and 3% to 11% for carcino-
mas [27, 29, 30]. A possible explanation for the heterogen-
eous results is the use of different types of tests for different
periods of follow-up. The higher detection rates are usually
reported in longer study periods. The need for at least three
annual consecutive tests has been supported by the fact that results were significantly lower on the first screening and approached their maximal range only after several rounds [11–14, 27].

The effectiveness of FOBT depends on stool rehydration (which increases sensitivity but reduces specificity), hemoglobin degradation (decreases sensitivity), and the presence of interfering compounds (such as animal meat and dietary peroxidases). False-positive results are 2% to 4% without rehydration and 8% to 16% in rehydrated samples, placing a heavy burden of diagnostic evaluation on a screening program [27, 29, 30].

**Cost-effectiveness of FOBT**

Screening the entire average-risk population for CRC would be very expensive. However, it is important for clinicians, health care payers and the public to realize that the cost of missing a curable cancer or of failing to prevent cancer by resecting pre-malignant polyps may be greater [21]. An average cost of US$7100–7800 per case of CRC detection was reported in several studies [29, 31].

Primarily using data from the Minnesota FOBT trial, health economists from the US National Cancer Institute and from the Office of Technology Assessment of the US Congress estimated that the cost of FOBT screening was less than US$15,000 per year of quality life gained [21]. On the other hand, the relatively low specificity and low predictive value of FOBT necessitates a large amount of upper and lower endoscopy. According to this calculation, it is equivalent to the accepted cost-effectiveness, to prevent a disease, with approximately US$25,000 per year of life saved [10]. This is still substantially less than the cost of many well-accepted preventative medical interventions. They concluded that screening for CRC is highly cost-effective and represents a good investment for US society. In part, because of these cost–benefit considerations, the US Congress provided colorectal cancer screening benefits, for the first time, for all Medicare patients beginning January 1, 1998. At the same time, one of the most alarming findings from this survey was that most of those who had not been screened reported that no medical professional had ever recommended screening to them [21].

Lieberman [5] calculated the cost-effectiveness of several CRC screening programs. The analysis included the cost of preventing one CRC-related death during a 10-year screening period. In a model with a 100% compliance rate, FOBT alone had the lowest cost per death prevented as compared with sigmoidoscopy (with or without FOBT), colonoscopy and barium enema. None the less, for a more realistic compliance rate of 50% or less, the estimated cost per death prevented was similar for FOBT and endoscopic screening modalities, while a higher cost was shown for barium enema. Furthermore, the authors have found that if colonoscopy costs are US$750 or less, one-time colonoscopy is more cost-effective than any other screening program at every level of compliance.

**Disadvantages**

In order for a screening test to be successful and cost-effective in large populations, the physicians and the subjects being screened must be compliant with screening recommendations. This is not the case with FOBT.

FOBT is usually performed by the patients and rarely during a rectal digital examination by the physician. Positive testing rates based on self-reported data were found to exceed rates based on computerized laboratory records by 14%. These data suggest cautious use of self-reported results [32].

Compliance is a major barrier to the achievement of optimal results. Average-risk population screening programs have reported compliance rates of 15% to 40% [10]. These rates gradually decrease over the years, although the efficacy of FOBT depends on the long-term performance of at least three consecutive annual examinations. Niv et al. [33] reported a high compliance rate of 71.5% for a 3-year annual FOBT among 3548 average-risk individuals between 40 and 75 years of age. During the 3-year screening period, the CRC incidence was similar in the FOBT group compared with refusers and controls that were never offered the screening test, but CRC stage and mortality were lower in the FOBT group. The beneficial effect of FOBT on decreased mortality remained during the 8-year follow-up period. This unique study cohort, consisting of a very stable and highly compliant population of kibbutz settlements, may explain the high compliance rate achieved in this trial. At the same time, their compliance decreased dramatically thereafter.

Compliance rates are further limited by the recommendations of dietary restrictions to reduce the number of false positives as a result of ingested peroxidases. A 3–14 day delay of Hemoccult sensa (HOS) test development, which allows breakdown of dietary peroxidases, has been suggested to overcome the need for dietary restrictions [24].

An important medical and legal issue is the approach to the patient with a positive FOBT and a clean colon on colonoscopy. Should an upper gastrointestinal tract evaluation be performed? Although there are no clear recommendations, this has been suggested by many studies, and is routinely performed by many physicians [24, 30, 34, 35]. Rocky et al. [30] examined a group of patients with positive FOBT who were referred for further evaluation. Upper gastrointestinal lesions were identified in 29% of the patients, while colonic lesions were identified in only 22% of cases. In another study, by the same author, he assessed healthy asymptomatic volunteers who drank small amounts of their own blood for 3–5 consecutive days. At least one positive HOS test was present in 50% to 100% of participants, depending on the ingested amount of blood (10–20 ml) [23]. Lurie and Welch [36] evaluated the pattern of diagnostic testing after an initial
positive FOBT. Their analysis suggested that only a minority of subjects screened received an appropriate diagnostic work up. In another study it was suggested that up to one-third of people who tested positive did not respond to requests for follow-up [37].

**Stool testing merits further consideration**

Stool testing merits further consideration, as its theoretical potential has not yet been achieved. Better tailored screening tools are needed that would exhibit the combined features of high sensitivity and specificity for early-stage cancers and large premalignant adenomas. There should be broad acceptability by the general population, affordability and safety. Neoplasm-specific DNA alterations have been well characterized [12, 13], and represent intriguing candidate markers for stool screening. DNA appears to be stable in stool samples [26] and amplification techniques permit detection of minute amounts of analyte. Several investigators have recovered mutant DNA in stools from patients with CRC or adenomas [20, 28–32]. A recently developed prototype stool assay system, the p-EXACT test (Exact Laboratories, Maynard, MA, USA), has been designed to target a spectrum of DNA alterations that occur with CRC and adenomas, with a sensitivity and specificity of almost 90%. This multi-component EXACT test assays point mutations at any one of 15 mutational hot spots on the K-ras, APC and p53 genes; BAT 26, a marker of microsatellite instability and highly-amplifiable or ‘long’ DNA (L-DNA) [38].

**Discussion**

The criteria for an optimal screening program include a common preventable disease, and a relatively sensitive, specific, safe and inexpensive test. The effectiveness of FOBT for CRC screening has been a subject of controversy. It is simple, safe, and low-priced, but it is limited by disappointing rates of compliance as well as poor sensitivity and specificity. The consequence of frequent false-positive tests results in a significant increase in cost, due to the many unnecessary gastroscopies and colonoscopies that are conducted. Moreover, a preventative program is worth while when the nature of its benefits outweigh its harm, and a screening program can cause harm. The harm to society may come indirectly by diverting funds from other beneficial projects [39]. Towler et al. [18] have performed a systematic review of the literature. It was estimated that 1000 asymptomatic persons (age >50) would have to be screened for ~10 years in order to prevent a single death from CRC. Hence, a more accurate and effective screening modality, with a higher impact on mortality, should be implemented.

In order for a screening test to be successful and cost effective in large populations, the physicians and the subjects screened must be compliant with screening recommendations. This is not the case with FOBT. Lurie and Welch [36] evaluated the pattern of diagnostic testing after an initial positive FOBT. Their analysis suggested that only a minority of screened patients received an appropriate diagnostic work up. In another study, it was suggested that up to one-third of people who tested positive did not respond to requests for follow-up [37].

Three randomized controlled trials have demonstrated reduced CRC mortality with usage of FOBT screening [11, 13, 14]. A meta-analysis pooling these three studies with new, unpublished data from a Swedish trial estimated a 16% reduction in CRC mortality (RR 0.84 with a confidence interval (CI) of 0.77 to 0.93). This reduction in mortality would increase to 23% if all patients were to adhere to the screening recommendations [18]. Much of the efficacy in the largest trial may reflect the application of colonoscopy to a large segment of the study population (Minnesota trial) [11]. Even more, the calculated cost per year of life saved is similar to that of the endoscopic screening of CRC [10].

Although compliance is a key factor in CRC mortality reduction by FOBT, the rates of compliance achieved in clinical trials are sub-optimal. The compliance in the community, outside the frame of a clinical study, is no doubt significantly lower. Data from the 1992 National Health Interview Survey indicated that only 17% of the population (≥50 years of age) performed FOBT within the past year [40]. In this range of less than 50% compliance rate, the calculated cost per CRC death prevented was similar for FOBT, sigmoidoscopy and colonoscopy. Moreover, if colonoscopy costs are $750 or less, one-time colonoscopy is more cost-effective than any other screening program at every level of compliance [5]. A recently published study [17] has found that even among compliant subjects who underwent a complete colonoscopy after returning three specimens for FOBT, the positivity rates of the test for advanced neoplasia and for any neoplasia were 23.9% and 11.7%, respectively. Moreover, sigmoidoscopy alone and combined with FOBT failed to identify 30% and 24% of advanced neoplasia, respectively.

In considering all the advantages and drawbacks of FOBT for CRC screening, we can conclude that this examination is undoubtedly better than no testing at all. However, an ~20% reduction in mortality is not satisfactory, in particular when compared with other screening modalities. FOBT is insufficient to be used alone for CRC screening. It might be used with sigmoidoscopy every 5 years. As of the year 2001, colonoscopy is still the best screening modality that significantly reduces CRC mortality. It seems almost unfair to offer FOBT when considerably higher rates of CRC prevention are achieved by colonoscopy carried out every 10 years (80% to 90%) [4, 5, 10]. A positive FOBT warrants colonoscopy and, if negative, gastroscopy followed by small bowel studies. A negative test does not give complete reassurance to the patient and physician, since most early colorectal neoplasia, especially small ones, are FOBT negative.
Recently, Inadomi and Sonnenberg [8] estimated the impact of CRC screening on life expectancy. They found that the potential extension of life through screening colonoscopy is 2- to 3-fold more than the extension achieved through flexible sigmoidoscopy or fecal occult blood testing.

Improved methods of cancer detection with newer technology look very promising. In particular, molecular biology tests such as the EXACT test are being tested in a large randomized clinical study headed by Ahlquist (Mayo Clinic) and sponsored by the National Cancer Institute (personal communication). It is hoped that further development of this technology could result in non-invasive screening tests with increased sensitivity and specificity.

The most important question from a public health standpoint is not which screening modality to use, but how we can improve access to screening for all members of society.

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