

Perspectives of Mass Colorectal Cancer Screening and Early Clinical Diagnosis

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ABSTRACT

With the aging and growth of world population and high prevalence of unhealthy behaviors and lifestyles, colorectal cancer (CRC) has become a big burden on global health. CRC is associated with multiple risk factors and its risk factors vary by population which makes intervention very difficult in the general population. Mass CRC screening is effective in reducing CRC mortality and incidence among asymptomatic individuals in the community although the magnitude of effectiveness is small due to many barriers. Based on current literature evidence and the fact of economic crisis, the editorial depicted the perspectives of mass CRC screening and early clinical diagnosis. A currently cost-effective and feasible Risk-Stratification-Based mass CRC screening protocol for CRC early detection and prevention is recommended and emphasized especially benefiting medically and economically underserved populations/areas. Existing issues for future research including urgent needs of serum biomarker and more efficient screening protocol for mass CRC screening are discussed.

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Key words: Perspectives; Colorectal Cancer Screening; Early Clinical Diagnosis; Serum Biomarker; Serum M2-PK

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INTRODUCTION

With the aging and growth of world population, high prevalence of unhealthy behaviors such as smoking and alcohol drinking, and increasing unhealthy food consumption and sedentary lifestyles including low physical activity and obesity/overweight, colorectal cancer (CRC) has become a big burden on global health^[1,2]. The etiology of CRC, however, is not completely understood. CRC is found to be associated with multiple risk factors and its risk factors vary by population which makes intervention very difficult in the general population. Research has consistently proven that screening asymptomatic individuals in the community can reduce the CRC mortality and incidence although the magnitude of effectiveness for each CRC screening test is relatively small in terms of mortality reduction^[3] due to many different barriers such as patient, test, and system/policy-related barriers^[4].

It is evident and necessary to consider mass CRC screenings, especially in medically and economically underserved populations/areas. Theoretically, CRC is an ideal disease for mass screening based on the following established criteria for a disease ideal for screening: CRC is serious with severe consequence such as death; treatment available for CRC is more effective at an earlier stage; CRC has a detectable preclinical phase (DPCP); and its DPCP is fairly long and prevalent because it often needs years for adenoma to develop into CRC which is true for most CRC patients in the population. The prevalence of DPCP of CRC and the number of cases detected by screening can be increased by screening high-risk populations of CRC. For example, we can target mass screening at people of ages from 40 to 75 years old and use simultaneous (multiple tests at the same time) and sequential (two-stage) testing design to screen high-risk populations from the asymptomatic individuals in the community in order to increase the efficiency of the mass CRC screening.

In the past decades, many countries have conducted mass CRC screenings. But why is CRC still a serious global health problem? How serious of a public health problem the disease is often depends on issues of cost-effectiveness and ethics of the screening. The main factors affecting the implementation of mass CRC screenings are how the screening is offered and processed, sensitivity and safety of the selected primary screening test, rate of unnecessary colonoscopy, expected mortality reduction, method of screening test result transmission, and cost^[3,5]. But population participation/compliance

is fundamental for the success of mass CRC screenings as for any disease screening program no matter how effective the screening is. Characteristics of the selected screening test directly affect compliance rates in mass CRC screenings. Pros and cons of potential CRC screening tests have been updated and summarized by Zhu and Zheng^[3].

In theory, the criteria for a test ideal for mass screening are that the test should be reliable; the test should be sensitive and specific; the test should be acceptable to the population being screened; and the test should be reasonably inexpensive and safe. Colonoscopy is not an ideal test for mass CRC screenings due to its inconvenience, expensiveness, time-consuming, and invasiveness with the risk of causing complications such as bleeding, perforation, and cardiopulmonary events which result in many asymptomatic people in the population not willing to have a colonoscopy. The low compliance rate influences its effectiveness in many mass CRC screening practices. For example, the compliance rate was 37.2% for iFOBT at the primary stage and 18.5% for colonoscopy at the secondary stage in our pilot screening program in China in 2004. Although colonoscopy has high sensitivity and specificity, it is not practical to consider a colonoscopy as a primary screening test to screen billions of asymptomatic population but rather as a follow-up screening and/or diagnostic test after primary screening in order to obtain a cost-effective screening. Because of the high compliance rate and feasibility, simultaneously testing both immunochemical fecal occult blood test (iFOBT) and high risk factors questionnaire (HRFQ) at a primary screening stage is the best choice for mass CRC screenings at this time. But the effectiveness for iFOBT and HRFQ in mass CRC screenings is limited by not high enough sensitivity and the potential missing cases of not-bleeding CRC and other colorectal disease lesions but not caught by HRFQ^[7]. It is necessary to update and emphasize a currently feasible protocol for CRC early detection and prevention and existing issues for future research including a promising new and more efficient screening protocol.

CURRENTLY FEASIBLE PROTOCOL FOR MASS CRC SCREENING AND EARLY CLINICAL DIAGNOSIS

Combination of HRFQ and iFOBT can be currently used as risk stratification tools to identify high-risk populations from the general population, especially medically and economically underserved populations, before a new more efficient screening test comes. Based on current available screening tests and knowledge of CRC etiology, a Risk-Stratification-Based mass CRC screening protocol can be used and is demonstrated in figure 1. This combination of sequential and simultaneous testing design protocol should maximally identify high risk populations from the general population without missing or minimally missing CRC cases and efficiently utilize limited resources on screening these high risk individuals of CRC. The sequential testing can be designed as using iFOBT and HRFQ simultaneously at the first/primary stage and if either the iFOBT or HRFQ is positive, a colonoscopy is recommended in the second stage of mass CRC screening. The fact that the combination of the simultaneous testing design increases the net sensitivity and the sequential testing design increases the net specificity greatly improves the efficiency of mass CRC screening which is much better than iFOBT or HRFQ alone. To include HRFQ in an active mass CRC screening program is an efficient strategy to identify high and average risk populations from the general population.

As expected the implementation of mass CRC screening in China

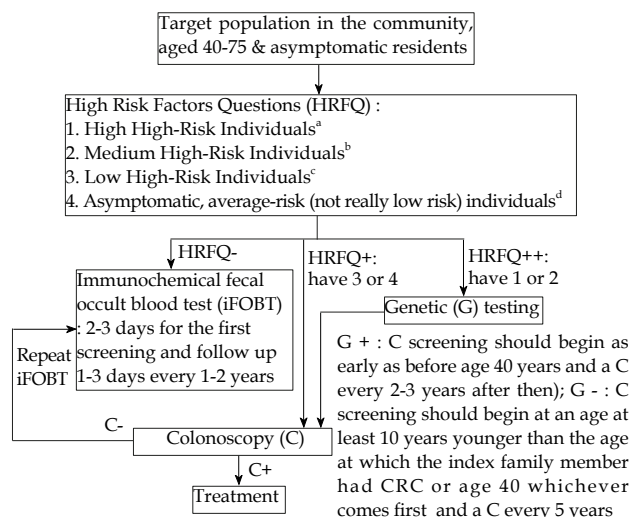


Figure 1 Flow chart of currently feasible mass colorectal cancer (CRC) screening Risk-Stratification-Based protocol, especially for medically and economically underserved populations/areas. ^a hereditary syndromes such as familial polyposis and Lynch syndrome associated with specific inherited gene mutations; ^b one or more family members having CRC without one of the hereditary syndromes; ^c personal history of chronic ulcerative colitis or Crohn colitis; ^d if meeting one of the three criteria: (1) History of cancer or intestinal polyp. (2) Two or more of the following: (i) chronic diarrhea; (ii) chronic constipation; (iii) phlegmatically blood feces; (iv) history of appendicitis or cholecystectomy; (v) history of chronic cholecystitis or cholecystectomy; and (vi) history of psychiatric trauma (e.g., divorce, death of 1st degree of relatives. (3) One or more of high-risk lifestyles: (i) smoking; (ii) heavy alcohol consumption; (iii) obesity; (iv) physical inactivity; and (v) diet high in animal food and low in vegetables and fruit. HRFQ-, HRFQ negative, answers to all questions in HRFQ are no; HRFQ+, HRFQ positive, either answer to question 3 (low high-risk individuals is recommended annual iFOBT after the first negative colonoscopy) or 4 (average-risk individuals is recommended iFOBT every 1-2 years after the first negative colonoscopy) in HRFQ is yes; HRFQ++, HRFQ strong positive, either answer to question 1 (high high-risk individuals) or 2 (medium high-risk individuals) in HRFQ is yes.

is obviously more difficult than in any other countries in the world. Due to a huge aging population, the target population for CRC screening is estimated about 0.43 billion (one-third of 1.3 billion) people age 50 and older in China. The current available resources such as number of physicians, colonoscopy centers and other related resources can hardly accomplish CRC screening in such a large population. Based on the facts of limited resources and current screening technology, the protocol of using iFOBT and HRFQ simultaneously at the first/primary stage has been innovatively used in China. From our mass CRC screening programs in both Jiashan county and Hangzhou city^[6,7], about 40% of adenomas, 50% of non-adenomatous polyps, and 30% of advanced neoplasms which diagnoses are confirmed by colonoscopy are identified by HRFQ and missed by iFOBT. Regardless of the compliance, 85% for HRFQ and 77% for iFOBT at the first/primary stage and at the secondary/late stage, 78% HRFQ-positive and 79% iFOBT-positive participants completing colonoscopy, the false positive rate is 85% for HRFQ and 77% for iFOBT. Although the CRC detection rate is not improved and the false positive rate is increased a little bit by HRFQ, it can be used as a complementary primary screening test for colorectal adenoma and non-adenomatous polyps to make up for a deficiency of iFOBT.

Based on the convenience, feasibility and safety, HRFQ can be used for both mass CRC screening and early clinical diagnosis to stratify high-risk populations: (1) People with hereditary syndromes such as familial polyposis and Lynch syndrome associated with specific inherited gene mutations can be stratified as high high-risk

individuals who should take a careful family history followed by genetic testing. Colonoscopy screening should begin as early as possible once becoming an adult like 20's, at least 10 years before age 40 years and a colonoscopy every 2-3 years is preferred; (2) People with one or more family members having CRC without one of the hereditary syndromes can be stratified as medium high-risk individuals who should take a careful family history. Colonoscopy screening should begin at an age that is at least 10 years younger than the age at which the index family member had CRC or age 40, whichever comes first; colonoscopy every 5 years is preferred; (3) People with personal history of chronic ulcerative colitis or Crohn colitis can be stratified as low high-risk individuals who should begin an annual three-day iFOBT as primary screening followed by a full colonoscopy if iFOBT is positive. If negative, routine screening (iFOBT annual, FS every 5 years, both iFOBT annual and FS every 5 years, or colonoscopy every 10 years) should be initiated before the onset of symptoms at age 50 years; and (4) The following people can be stratified as asymptomatic, average-risk (not really low risk) individuals^[3] : aged 40-75 years having one or more of the following: (1) A personal history of cancers or intestinal polyps; (2) Two or more of the following: (i) chronic diarrhea; (ii) chronic constipation; (iii) phlegmatically blood feces; (iv) history of appendicitis or appendectomy; (v) history of chronic cholecystitis or cholecystectomy; (vi) history of psychiatric trauma (e.g. divorce, death of 1st degree of relatives); and (3) high-risk lifestyles: (i) smoking; (ii) heavy alcohol consumption; (iii) obesity; (iv) low physical activity; and (4) diet high in animal food and low in vegetables and fruit. Screening for these individuals can be the same as low high-risk individuals described above and the screening frequency can be flexible. Those individuals not identified by any above stratification should be encouraged to continue routine HRFQ and iFOBT every 1-2 years screening from age 50 to 75 years. The recommended flow chart of currently feasible mass CRC screening protocol, especially for medically and economically underserved populations, is shown in figure 1. For medically and economically underserved populations, the iFOBT combing with a HRFQ can be recommended for 2-day sample tests for the first screening and follow up once (1-day sample test) every 1-2 years. For some populations in the developed areas or countries with sufficient medical resources and good economic support, screening frequency and test could be flexible. The iFOBT can be recommended for 3-day sample tests for every 1-2 years. Or colonoscopy might be recommended as primary screening test for them. Considering the average life expectancy is getting longer in many countries, the screening age is appropriately extended to 75 years old.

Uniform, up-to-date guidelines on mass CRC screening practices should be used by physicians and other related stakeholders. Attention to family history and personal risk assessment is needed. Regular workshops to educate physicians and other related stakeholders to utilize and be aware of the CRC screening tests should be established. Addressing about patient and system-related barriers with individuals should help improve CRC screening compliance. Also it may be useful for physicians to recommend risk-reduction strategies. Considerable epidemiologic evidence shows that environmental factors such as smoking, heavy alcohol use, obesity, physical inactivity, and diets high in animal food and low in vegetables and fruit may increase the risk of CRC, any intervention to reduce exposure to these environmental risk factors would be helpful in reducing some incidence of CRC. Nevertheless, patients should understand risk-reduction strategies do not take the place of effective screening.

ISSUES FOR FUTURE RESEARCH

There are a few issues needed to be solved in future research. (1) Low compliance to current mass CRC screenings. Researchers need to find a new test with high compliance in order to increase the effectiveness of mass CRC screenings; (2) Limited resources available for implementation of mass CRC screening, especially under the current worldwide economic crisis; (3) To develop a new better non-invasive screening test with high sensitivity that will lead to higher compliance rates is critical to solve the above issues. If a new inexpensive, convenient, and safe screening test with high sensitivity is developed, then compliance rate would be high and limited resources would be enough for a cheap and more efficient screening test. In the long run, the health care burden from colorectal cancer will be reduced or minimized.

The huge burden of the current health care, especially under the worldwide economic crisis, demands cheap and more effective screening tests such as serum biomarkers for CRC early detection. Therefore, there is a growing need to develop simple, fast, economic, effective, and more acceptable serum biomarker tests for mass CRC screening. From our pilot study, serum biomarker Pyruvate Kinase Isoenzyme M2 (M2-PK) which is a tumor M2-PK, a dimeric form of M2-PK determined by Sandwich ELISA method and different from other non-tumor M2-PK, is promising to be developed as a primary mass CRC screening. Any serum biomarker with high sensitivity should be ideal as a primary test for mass CRC screening due to a high compliance which is fundamental for the success of a mass CRC screening. In our pilot study^[3,8], results showed that the sensitivity reached 100.00% for CRC when the cut-off value of serum tumor M2-PK was 2.00 U/mL. The price is inexpensive, about \$5 per person per procedure. It is a cheap, convenient, safe, and efficient test with a high sensitivity and compliance for CRC primary mass screening. Considering the fact that serum tumor M2-PK like Carcinoembryonic antigen (CEA) is expressed in most cancer cells and undifferentiated tissues and not an organ specific tumor biomarker which specificity is not high, ranging from 41% to 74% at the cut-off value changing from 2.00 to 4.00 U/mL in our pilot study although specificity is usually not considered as important as sensitivity in a primary screening, it needs to be extensively investigated in many different population settings like different races, with a big sample size, and medically and economically underserved populations. Also different cut-off values of serum tumor M2-PK and or combinations (either simultaneously or sequentially) with other serum biomarkers such as serum CEA need to be extensively investigated and determined in different population settings in order to best utilize the value of serum tumor M2-PK in mass CRC screenings.

Figure 2 describes a flow chart of a promising new and more

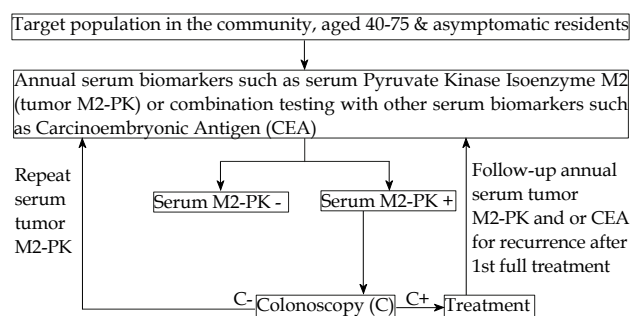


Figure 2 Flow chart of a promising new colorectal cancer mass screening and early clinical diagnosis protocol - serum biomarker such as tumor M2-PK as primary screening test and colonoscopy as secondary screening diagnosis test. Abbreviations: -: negative; +: positive; C-: colonoscopy negative; C+: colonoscopy positive.

efficient mass CRC screening and early clinical diagnosis protocol - serum biomarker such as tumor M2-PK as primary screening test and colonoscopy as secondary screening/diagnosis test. First, to use serum tumor M2-PK as a primary screening test avoids inconvenience, expensive costs, and colonoscopy-related complications during CRC screening, which would increase the compliance- the key to a successful mass CRC screening program. Second, serum tumor M2-PK has high sensitivity -100% at the cut-off value of 2.00 U/mL which guarantees almost no CRC cases would be missed at the first stage of screening. Also other serum biomarkers such as serum CEA can be considered to test either simultaneously or sequentially with serum tumor M2-PK in order to increase either the net sensitivity or net specificity, respectively, which depends on the needs of the mass CRC screenings. Third, almost all cases would be diagnosed by colonoscopy due to its high sensitivity and high specificity in the follow-up or secondary stage of screening. Thus the effectiveness of mass CRC screening program should be improved tremendously. Fourth, if the first colonoscopy is negative, then serum tumor M2-PK or combinations with other serum biomarkers such as CEA can be easily repeated every year after the first screening or screening for other cancers should be recommended for those participants if their serum M2-PK is above a certain level. For example, in our pilot study, if the tumor serum M2-PK is above 4.00 U/mL and the first colonoscopy is negative, screening for cancers should be recommended. And if the first colonoscopy is positive, then serum tumor M2-PK can be used as a follow-up surveillance biomarker for recurrence after the first full treatment. In the long run, the health care burden from CRC would be minimized due to low CRC incidence and mortality in the population which is the beneficial outcome of a successful mass CRC screening program.

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