

What is the optimal colorectal cancer screening program for an average-risk population?

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Colorectal cancer (CRC), one of the most commonly diagnosed cancers, is a major cause of cancer-related death in the world (1). To reduce CRC mortality, the implementation of “appropriate” CRC screening is essential. Thus, it is important to define what constitutes “appropriate” CRC screening. First, it must be effective and safe. There is strong evidence that the fecal occult blood test (FOBT) and sigmoidoscopy are effective CRC screening tools and their value in reducing CRC mortality has been proven in several randomized controlled trials (RCTs) (2-10). Despite the lack of strong evidence from RCTs, an increasing number of high-quality studies (test characteristic studies, prospective cohort studies, and case-control studies) have demonstrated the effectiveness of other screening modalities including the fecal immunochemical test (FIT), colonoscopy, multi-targeted stool DNA testing (FIT-DNA), and computed tomography colonography (CTC) (11-14). Based on these studies and others, the above-mentioned multiple screening modalities are now recommended for CRC screening in a US Preventive Service Task Force (USPSTF) Recommendation Statement (15). Despite the recommendations for the multiple modalities, there have been few direct comparisons of the benefits and limitations of these modalities. Thus, the optimal CRC screening strategy, including the selection of screening modalities, is still unclear and further investigation on this issue is required.

To implement “appropriate” CRC screening programs,

other parameters in addition to effectiveness and safety should be considered. The optimal age for screening and the burden of screening are two of the important issues to be investigated. The ages at which to start and stop average-risk screening should be clarified. Without specifying the ages, confusion can occur when conducting CRC screening. For instance, in Japan, the starting age for population-based CRC screening is set at 40 years, but the upper limit of the screening age is not specified. Thus, in the elderly population, confusion is increasingly observed in the management of CRC screening. With regard to the burden of screening, the required number of screening examinations, particularly for colonoscopies, is an essential parameter that should be specified. Even with an effective CRC screening program, if the required number of colonoscopies is beyond the nationwide capacity, the screen cannot be implemented. CRC screening should be planned and implemented within the total nationwide capacity of colonoscopies. However, except in a limited number of countries, the colonoscopy capacity is undefined. Currently in Japan, the capacity for colonoscopies is not fully understood. However, recently, the Japan Gastroenterological Endoscopy Society started a Japan endoscopy database project aiming to obtain important nationwide endoscopy data, and the database is expected to be helpful for estimating the Japanese colonoscopy capacity.

A recent study, “Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies” by

AB Knudsen *et al.* published in the *JAMA*, examined the above-mentioned important issues for implementing an “appropriate” CRC screening program by performing microsimulation analysis (16). The objectives of the study were to estimate the optimal age for CRC screening and identify recommendable CRC screening strategies. This modeling study was conducted by leading experts in the field by request from the USPSTF to assess the benefits (life-years gained: LYG), burden (the required number of colonoscopies), and harms (the number of complications from colonoscopy) of various screening strategies using gFOBT, FIT, FIT-DNA, sigmoidoscopy, colonoscopy and CTC for the general US population. Microsimulation models of CRC have been used to assess long-term outcomes of CRC screening, including benefits, harms, burden, and cost-effectiveness, in many previous studies and their usefulness is now well documented (17). One of the strengths of this study is that the analyses were performed using three independent representative models of CRC: Simulation Model of CRC (SimCRC), Microsimulations Screening Analysis (MISCAN), and Simulated Population model for Incidence and Natural History (CRC-SPIN) (18-20). Based on the findings for LYG and the required number of colonoscopies from the model analysis, it was concluded that the reasonable ages to start and end CRC screening in the average-risk population are 50 and 75 years, respectively. The model analysis showed that starting screening earlier (45 years) could be more effective with a better balance between LYG and colonoscopy burden; however, because of the lack of empirical evidence, starting at 50 years was recommended. In terms of the recommended screening strategies from 50 to 75 years, in the model study, the following four strategies yielding similar benefits and a comparable balance between benefits and burden were identified: colonoscopy every 10 years, sigmoidoscopy every 10 years with annual FIT, CTC every 5 years, and annual FIT.

Although the results obtained from this model study regarding the optimal age for screening and recommended screening strategies are very valuable, they should be interpreted with careful attention to the limitations involved in the study as specified by the authors. Herein, we would like to highlight some of the important limitations. First, the results of this model study were obtained with the assumption of 100% adherence to screening. However, full adherence to a screening program is difficult to achieve, and adherence can vary for different screening strategies in the real world. The results from the model analysis

based on a different adherence rate for each screening strategy would be informative. Also, further evaluation of the difference in adherence for each type of screening and how to improve it is required. Second, the fact that quality of life (QOL) was not considered in the evaluation of the benefits of screening is also a limitation. There are very few studies with high-quality data on the QOL related to CRC and CRC screening, thus, it is difficult to include QOL in the assessment. However, if QOL can be included in the assessment and QOL-adjusted LYG can be used as a measure of screening benefits, it may be more informative. Further studies on QOL related to CRC and CRC screening are warranted. In response to this issue, recently our group investigated the QOL of CRC patients undergoing endoscopic treatment and laparoscopic-assisted colectomy (21). Third, although the three microsimulation models of CRC used in the analysis are well developed and validated, they are still not perfect and there remains room for improvement. Although all models are based on the concept of the adenoma-carcinoma sequence, it is known that there are other pathways involved in the development of CRC, including the serrated pathway and *de novo* pathway (22,23). Once additional high-quality data is collected on other pathways in the future, it should be incorporated into the models.

When interpreting these results, we should also keep in mind that the target of the study was the general US population. Thus, we cannot apply the recommendations from this study directly to CRC screening in other countries. In each country, further evaluation and modifications based on their own country's data and evidence is necessary. For instance, in Japan, recently our group investigated the effectiveness and cost-effectiveness of CRC screening for the Japanese population by using Japanese clinical data and performing a microsimulation analysis. The results indicated that more frequent use of colonoscopy could be more effective and cost-effective than the current population-based CRC screening with annual FIT in Japan (24). As evaluated in this Japanese study and many previous studies, “cost-effectiveness” is also an important factor for population-based screening, and microsimulation analysis can be very helpful for evaluation of cost-effectiveness (17,24).

Finally, the fact that more data are still required for several screening modalities to evaluate their long-term effect in CRC screening is not negligible. Although the above-mentioned high-quality modeling study recommends colonoscopy every 10 years and CTC every 5 years as

part of a CRC screening program, more data need to be collected on the mortality reduction effect achieved as a result of these screening strategies. Several RCTs evaluating the long-term effectiveness of screening colonoscopies are ongoing, and the results of these studies are eagerly anticipated. Additionally, evaluation of other screening strategies that were not evaluated in the modeling study, including capsule colonoscopy (25) and micro-RNA, is required, and further development of new modalities is also expected. A more personalized screening strategy based on risk stratification could also be an important part of a future optimal screening strategy. To establish an optimal CRC screening program from the perspectives of benefits, burdens and harms, there are still several issues to be clarified, and the efforts and collaborations by investigators from various fields and countries will be indispensable.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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