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SPECIAL REPORT

The IARC Perspective on Colorectal Cancer Screening

Béatrice Lauby-Secretan, Ph.D., Nadia Vilahur, Ph.D., Franca Bianchini, Ph.D., Neela Guha, Ph.D., M.P.H., and Kurt Straif, M.P.H., M.D., Ph.D., for the International Agency for Research on Cancer Handbook Working Group

Colorectal cancer, which is the third most common cancer in men and the second most common in women, represents almost 10% of the annual global cancer incidence.[1] Incidence rates of colorectal cancer show a strong positive gradient with an increasing level of economic development.[2] Even so, the net 5-year rate of survival decreases with lower levels of income, with rates reaching 60% in high-income countries but falling to 30% or less in low-income countries.[3]

Established risk factors for colorectal cancer include consumption of processed meats,[4] consumption of alcoholic beverages,[5] tobacco smoking,[5] and excess body fat,[6] whereas consumption of dietary fiber and dairy products and increased levels of physical activity decrease the risk.[7,8] In addition, certain subgroups of the population are at increased risk owing to genetic predisposition (e.g., the Lynch syndrome), a family or personal history of colorectal neoplasia, or medical conditions (e.g., inflammatory bowel disease) that have been associated with colorectal cancer.

Colorectal cancer can be classified on the basis of the location within the large bowel, histologic characteristics, and molecular features. Advanced adenomas — in particular, those measuring more than 10 mm in diameter — are the most well-known precursor lesions of colorectal cancer.[9] Screening aims to reduce the risk of death from colorectal cancer through early detection and the rate of complications associated with detection of cancer at a later stage. Such screening also aims to reduce the incidence and mortality of colorectal cancer through detection and removal of precancerous lesions. Colorectal cancer screening is available in many countries with high and upper-middle incomes worldwide and is delivered by organized programs or through opportunistic screening. Participation rates in such screening are highly variable among countries and settings[10] but have typically been below 40%. Insurance status and access to primary care are the main determinants of participation. Additional obstacles include costs, logistic challenges, lack of provider involvement, language barriers, cultural beliefs, and lack of awareness of colorectal cancer screening.[11,12]

There are several methods available for colorectal cancer screening. Stool-based tests to detect blood include the guaiac fecal occult blood test and the more sensitive fecal immunochemical test (FIT).[13] Endoscopic methods, which use optical approaches to directly examine the rectum and colon, include sigmoidoscopy and colonoscopy.[14] Colonoscopy is used both as a primary screening tool and as follow-up for persons who have tested positive with other screening methods. In addition, computed tomographic (CT) colonography, an imaging method based on scanning technology, has been developed as a less invasive visualization technique for colorectal cancer screening.[15] Newer techniques that have recently emerged but have not been widely tested are based on visual inspection (e.g., video capsule endoscopy) or the analysis of biomarkers in stool (e.g., multitarget-stool DNA), in blood (e.g., methylated septin 9 DNA), or in breath (e.g., volatile organic compounds and various markers of protein, RNA, and DNA).

We reviewed the published evidence from randomized, controlled trials, observational studies, and modeling studies assessing stool-based, endoscopic, and CT colonography–based screening methods and evaluated outcomes with respect to preventive effects, adverse effects, and the balance of benefits and harms in average-risk populations of men and women combined. (Details regarding the working procedures that were used for conducting the review and a list of the members of the International Agency for Re-

Table 1. Evaluations of Colorectal Cancer Screening with Stool-Based Tests, Endoscopic Methods, and Computed Tomographic (CT) Colonography.*

Screening Technique	Strength of Evidence Regarding Colorectal Cancer Screening		
	Reduction in Incidence	Reduction in Mortality	Benefit–Harm Ratio
Stool-based tests			
Screening every 2 yr with guaiac test without rehydration	Suggestive of a lack of effect	Sufficient	Sufficient
Screening every 1 or 2 yr with higher-sensitivity guaiac test (with rehydration)	Limited	Sufficient	Sufficient
Screening every 2 yr with FIT	Limited	Sufficient	Sufficient†
Endoscopic techniques			
Single screening with sigmoidoscopy	Sufficient	Sufficient	Sufficient
Single screening with colonoscopy	Sufficient	Sufficient	Sufficient‡
CT colonography			
Single screening with CT colonography	Limited§	Limited§	Inadequate

* The finding of sufficient evidence applies only to settings in which it is assumed that screening, along with treatment and follow-up, can be delivered with high quality. FIT denotes fecal immunochemical test.
† A variety of qualitative and quantitative FIT tests are available, with wide ranges of sensitivity and specificity. The net balance of benefits and harms depends on the cutoff level for positivity.
‡ A minority of the members of the International Agency for Research on Cancer (IARC) Handbook Working Group considered that the evidence is limited because of the variability of the effect estimates, the risks associated with colonoscopy, and the inherent limitations in extrapolating conclusions from data regarding screening with sigmoidoscopy.
§ The evaluation of limited evidence regarding CT colonography applies to the reduction in incidence or mortality (one single evaluation). A minority of the members of the IARC Handbook Working Group considered that the evidence is inadequate because of the lack of randomized trials or observational studies (including those with repeated CT colonography screening) and lack of data regarding risks.

search on Cancer [IARC] Handbook Working Group are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

In cases in which data from randomized trials of the effect of a particular screening test on colorectal cancer mortality and incidence were not available, evidence regarding a similar screening test for which a reduction in colorectal cancer mortality or incidence has been shown (e.g., FIT instead of guaiac testing or colonoscopy instead of sigmoidoscopy) or from comparative studies of test performance (e.g., CT colonography instead of colonoscopy) was considered. Evidence regarding the above-mentioned newer techniques was considered insufficient to make an evaluation.

Here, we briefly summarize the evaluation of the scientific evidence, as reviewed by the Handbook Working Group (Table 1). The full report will be published as volume 17 of the IARC Handbooks of Cancer Prevention. It is noteworthy that the majority of studies that were reviewed had been conducted in settings with middle or high incomes, in which the incidence of colorectal cancer is generally high; in asymptomatic, average-risk populations (typically, between the ages of 50 and 70 years); and under conditions in which colorectal cancer screening, including subsequent follow-up and treatment, can be delivered with high quality. The extrapolation of the conclusions to different settings needs to take into account these and other context-related specificities (e.g., the level of health-system development).

STOOL-BASED TESTS FOR OCCULT BLOOD

BENEFICIAL EFFECTS OF GUAIAC TESTING

We reviewed all the studies that assessed the effect of screening every 1 or 2 years with the guaiac fecal test in reducing the incidence of colorectal cancer, mortality associated with the

disease, or both. These studies included 5 randomized trials that were performed in North America or Western Europe[16-20] and 10 observational studies conducted in screening settings that were performed in different geographic regions.[21-30] In these studies, the investigators performed guaiac testing either without rehydration or with hydration, with the latter test having a higher sensitivity (Table 1).

On the basis of the results of two randomized trials, two large cohort studies with up to 11 screening rounds, and one case–control study,[16,19,23,24,26] there is sufficient evidence that screening every 2 years with the guaiac test without rehydration reduces colorectal cancer mortality, as does screening every 1 or 2 years with the higher-sensitivity guaiac test.[17,20,25] In the randomized trials, the relative risk of death from colorectal cancer was significantly lower among the persons with a positive test result who had undergone guaiac testing coupled with colonoscopy than among controls (no screening); the relative risks were 9 to 14% lower with guaiac testing without rehydration and 16 to 32% lower with higher-sensitivity guaiac testing.

The evidence suggests a lack of effect of screening every 2 years with the guaiac test without rehydration in reducing the incidence of colorectal cancer on the basis of three randomized trials and one cohort study after 11 screening rounds.[16,18,19,24] In addition, there is limited evidence that screening every 1 or 2 years with the higher-sensitivity guaiac test reduces such incidence, on the basis of one randomized trial with 18 years of follow-up.[31]

BENEFICIAL EFFECTS OF FIT

To our knowledge, no randomized trials of FIT with data on incidence or mortality outcomes have been performed, but the findings from observational studies in screening settings were highly consistent. Three cohort studies, including one incidence-based mortality study, showed relative risks of death from colorectal cancer that were 10 to 40% lower among persons who had undergone FIT screening than among controls.[32-34] One ecologic study in Italy that compared areas that had early implementation (2002–2004) of an organized program of FIT screening every 2 years versus late implementation (2008–2009) also showed a lower relative risk of death from colorectal cancer in the area where screening was introduced first than in the area with later implementation.[35] Overall, there is sufficient evidence that screening every 2 years with FIT reduces colorectal cancer mortality. This evaluation also takes into account evidence from randomized trials of guaiac testing, from which we can infer that FIT should be at least as good as guaiac testing in reducing colorectal cancer mortality, and evidence from randomized trials showing that FIT performed better than guaiac testing for the detection of advanced adenoma and colorectal cancer.

The evidence was deemed to be limited with respect to lowering the incidence of colorectal cancer. Small-to-moderate reductions in cumulative incidence were observed in two cohort studies after three rounds of FIT performed every 2 years[33,34] and in one ecologic study conducted in Italy.[36]

POTENTIAL HARMS AND BENEFIT–HARM RATIOS

Potential harms of screening with stool-based tests for occult blood are related to psychological harms of screening per se and of receiving a positive test result, harms that were reported to be mild and transitory.[37,38] In addition, unnecessary referrals and medical harms linked to follow-up colonoscopy and surveillance after a positive test can occur. In modeling studies, all stool-based tests for occult blood provided gains in quality-adjusted life-years, as compared with no screening, especially FIT and higher-sensitivity guaiac testing.[39] Overall, there is sufficient evidence that the benefits outweigh the harms of colorectal cancer screening with any type of stool-based test for occult blood.

ENDOSCOPIC METHODS

Four large, randomized trials of sigmoidoscopy screening — three in Europe and one in the United States[40-43] — have been performed. In all the studies that evaluated the relative risk of colorectal cancer, such incidence was significantly lower (18 to 26%) among persons who had undergone sigmoidoscopy screening than among those who had not; the relative risk of death from colorectal cancer was also significantly lower (22 to 31%) in all but one study.[43] An extended follow-up of one trial up to 17 years showed a persistently significant lower relative risk of 26% in colorectal cancer incidence and of 30% in colorectal cancer mortality in intention-

to-treat analyses.[44] Four randomized trials of colonoscopy are currently in progress, but data on the effect on colorectal cancer incidence or mortality are not yet available.

A large number of observational studies were available for review, but only those that were performed in a screening setting (conducted mainly in the United States) were included for evaluation. Two cohort studies[45,46] provided estimates on colorectal cancer incidence, mortality, or both associated with sigmoidoscopy, and five cohort studies[46-50] provided such data associated with colonoscopy. In addition, case–control studies, including several studies involving more than 2000 persons, provided risk estimates for sigmoidoscopy (nine studies) and colonoscopy (five studies). In most cohort and case–control studies, the relative risks of incidence and death were significantly lower among persons who had undergone either sigmoidoscopy or colonoscopy than among controls, although relative risks varied greatly among the studies. The most recent meta-analysis of observational studies estimated risk reductions in both incidence and mortality of almost 70% with colonoscopy and almost 50% with sigmoidoscopy. The effect was consistently stronger in the distal colon than in the proximal colon.[51]

There is sufficient evidence that a single screening with sigmoidoscopy or colonoscopy reduces colorectal cancer incidence and mortality (Table 1). In addition to considering the consistent results from the observational studies of colonoscopy, this evaluation also takes into account evidence from randomized trials of sigmoidoscopy screening, since a full colonoscopy, by definition, includes a sigmoidoscopy, and if we assume that there will be similar false negative rates for both procedures, colonoscopy will be at least as effective as sigmoidoscopy in detecting advanced adenomas and colorectal cancer. Currently, there is insufficient evidence to assess the benefit of subsequent rounds of endoscopic screening.

Similar to stool-based tests for occult blood, endoscopic screening may generate psychological harms, along with unnecessary referrals after positive results on sigmoidoscopy. In addition, endoscopy may provoke serious medical harms, of which bleeding and perforation are the most frequent, although such adverse events remain uncommon, with each event occurring in 0.01 to 0.05% of colonoscopy procedures.[52] The proportion of overdiagnosis of cancer from endoscopic screening is uncertain.

In modeling studies, sigmoidoscopy and colonoscopy both provide gains in quality-adjusted life-years, as compared with no screening.[53] Overall, there is sufficient evidence that the benefits of a single screening with sigmoidoscopy outweigh the harms. The consensus was that there is sufficient evidence that the benefits of a single screening with colonoscopy also outweigh the harms, when screening can be delivered with high quality. A minority of the expert panel members considered that the evidence is limited because of the variability and the related limited accuracy of the effect estimates, the harms associated with colonoscopy, and the inherent limitations in extrapolating findings regarding sigmoidoscopy to evaluate colonoscopy.

CT COLONOGRAPHY

To our knowledge, no published, randomized trials have assessed the effect of CT colonography screening on colorectal cancer incidence or mortality. One randomized trial[54] and four tandem studies[55-58] with consecutive or parallel screening of asymptomatic persons compared rates of adenoma detection with CT colonography versus those with colonoscopy and were considered to be informative for the evaluation. In the tandem studies (a comparison study in which the same person was screened sequentially with two methods), the detection rates of advanced neoplasia (advanced adenoma or cancer) were similar with both techniques; in the randomized trial, detection rates with CT colonography, as compared with colonoscopy, were similar for colorectal cancer but were lower for all advanced adenomas (5.6% vs. 8.2%) and for advanced adenomas measuring at least 10 mm (5.4% vs. 6.3%); this difference disappeared after adjustment for participation rate.

Potential harms that are associated with CT colonography include radiation-induced effects, the downstream effects from detection of extracolonic findings,[59] and the potential harms of follow-up colonoscopy. On the basis of these data, there is limited evidence that a single screening with CT colonography reduces colorectal cancer incidence or mortality. A minority of the expert panel members considered that the

evidence is inadequate because of the lack of randomized trials or observational studies with incidence or mortality as end points, the lack of studies with repeated CT colonography screening, the fact that data regarding only test performance and adenoma detection rates were available, and the wide extrapolation needed from the known detection rates of lesions to an expected reduction in colorectal cancer incidence or mortality in a screening setting. Finally, there is inadequate evidence that the benefits of a single round of screening with CT colonography outweigh the harms.

COMPARATIVE EFFECTIVENESS OF SCREENING TECHNIQUES

Comparisons of reductions in colorectal cancer incidence and mortality with stool-based methods versus endoscopic methods were available from network meta-analyses (indirect comparisons of studies of screening versus no screening). One meta-analysis of nine randomized trials[60] showed that sigmoidoscopy performed better than guaiac testing in reducing colorectal cancer incidence but not mortality. Another meta-analysis that included both randomized trials and observational studies in screening settings[61] showed that colonoscopy was more effective than sigmoidoscopy and guaiac testing in reducing colorectal cancer mortality, although the quality of the evidence was low because of the heterogeneity in study designs and inherent biases in such comparisons. In addition, when comparing the performance of a single screening round, endoscopic techniques, especially sigmoidoscopy, generally yielded higher detection rates of advanced neoplasia than one-time stool-based tests for occult blood.[62-65] However, recent data suggest that detection rates of advanced neoplasia with FIT performed every 2 years over five consecutive screening rounds were similar to those with one-time colonoscopy.[66] Taken together, the evidence was considered to be insufficient to evaluate the comparative effectiveness of the available screening techniques.

In conclusion, there is sufficient evidence that screening for colorectal cancer with currently established stool-based tests (guaiac testing and FIT) and lower endoscopy (sigmoidoscopy and colonoscopy) reduces the risk of death from colorectal cancer and that the benefits outweigh the harms associated with each type of screening. Evidence from comparative effectiveness studies to evaluate one test over another was inconclusive.

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From the International Agency for Research on Cancer, Lyon, France (B.L.-S., N.V., N.G., K.S.); and the German Cancer Research Center, Heidelberg (F.B.). Address reprint requests to Dr. Lauby-Secretan at the International Agency for Research on Cancer, IARC Handbooks Group (ESC/IHB), 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France, or at secretanb@iarc.fr.

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