Screening is a public health service wherein people of a defined population, who do not perceive that they are at risk for, or are already affected by, a disease or its complications, are asked a question or offered a test. This process identifies those who are more likely to be helped than harmed by further tests or treatment and reduces the risk of a disease or its complications.

- As screening targets apparently healthy people, it has important ethical differences from clinical practice. Screening methods are not hundred percent safe and it is important that physicians and the lay public recognize this. A balance between safety and sensitivity has to be maintained. Screening has the potential to save lives or improve quality of life through early diagnosis of serious conditions, by reducing the risk of developing a condition or its complications. Screening cannot be taken as a guarantee of complete protection. In any screening program, there is an irreducible minimum of false positive results and false negative results. Screening should be considered risk reduction rather than risk elimination. Following the discussion for the screening of individual cancers the statement of the National Cancer Institute (www.nci.nih.gov) is mentioned.

Screening of Gastric Cancer

Screening of gastric cancer in asymptomatic persons may increase the chance of detecting early cancer and hence may improve the overall survival. In a study from Japan, a screening program of gastric cancer using seven – film photo urography followed by endoscopic biopsies in suspicious cases, found that 40 % to 60 % of cancers diagnosed were early cancer, with no lymphatic metastasis. This program has been attributed as one of the reasons for the decline in stomach cancer mortality in Japan. However, a formal randomized study to evaluate the effectiveness of this screening strategy is lacking. As the incidence of gastric carcinoma in many developed countries is low, routine population based screening program cannot be adopted. In these countries, screening may be targeted to high – risk persons only, e.g. those with family history of gastric cancer, chronic atrophic gastritis, previous gastric surgery, or pernicious anemia.

Biochemical markers to identify those at risk of developing gastric carcinoma include low serum pepsinogen I, which correlates with corpus atrophy, has been found to be significantly associated with
gastric cancer. An elevated serum gastrin level has also been used in the screening of severe atrophic gastritis, but has a low sensitivity (30%), thus precluding its use as a screening tool. The other potential serologic marker that may be used in screening of gastric cancer is H. pylori antibody testing. One study showed that no screening test (including H. pylori and CagA serology, and gastrin) was sensitive and specific enough to be used for the screening of chronic atrophic gastritis in populations with a high gastric cancer incidence.

Summary of Evidence by The National Cancer Institute
There is insufficient evidence to establish that screening would result in a decrease in mortality from gastric cancer in the U.S. population. Endoscopy is sometimes used to screen for gastric cancer. There are serious but uncommon side effects associated with endoscopy, which may include the following: perforation, cardiopulmonary events, aspiration pneumonia, and bleeding requiring hospitalization.

Screening for Esophageal Cancer
High – incidence areas, such as in northern China, may merit endoscopic screening in the general population. Screening in areas with low prevalence cannot be advocated. However, screening and surveillance endoscopic programs may be applied to certain clinical situations, such as patients with tylosis, achalasia, and head and neck cancer.

Surveillance of Barrett’s Metaplasia and Dysplasia
Two important variables for the selection of a particular surveillance strategy in a decision model comparing no surveillance with surveillance every 1 to 5 years with surgical resection for high – grade dysplasia or cancer were found. These variables are the incidence of cancer arising in Barrett’s esophagus and the quality of life after surgical resection. There are no definitive surveillance recommendations, but certain guidelines from leading expert centers may help to guide clinical practice. Endoscopic biopsies taken systematically that are negative for histological dysplasia and are without cytometric and cytologic abnormalities should lead to repeat endoscopic evaluation at 2 – year intervals. If high – grade dysplasia is detected histologically without any endoscopic abnormalities, then early repeat endoscopy with multiple biopsies should be pursued to document the extent of high – grade dysplasia and to exclude coexisting cancer. Treatment recommendations for high – grade dysplasia need to be individualized. Surgical resection will be guided by the patient’s performance status, coexisting illnesses, compliance with endoscopic surveillance, and surgical teams’ experience with surgical resection. For patients with high – grade dysplasia who do not opt for surgical resection but who would do so if cancer were diagnosed, then endoscopic surveillance biopsies should be repeated 3 months after the initial two endoscopies and at 6 – month intervals thereafter. Adenocarcinoma can develop in small or large areas of high – grade dysplasia, and thus systematic biopsies must be taken.

In a study of using balloon cytology in the surveillance of Barrett’s esophagus for dysplasia, adequate columnar epithelium was obtained in 52 of 63 patients with balloon cytology and in 59 of 61 patients with brush cytology. The detection rate of balloon cytology for abnormal cells in patients with adenocarcinoma, and high – grade dysplasia, was not different from the pick up rate with brush cytology. The authors concluded that balloon cytology may be adequate and cost effective for the detection of high – grade dysplasia or carcinoma, provided sampling is adequate and a more abrasive balloon could be pursued. More studies are needed before any recommendation can be made.

Promising markers to identify patients at risk of developing high grade dysplasia include measurement of small intestinal brush border enzymes such as a sucrose isomaltase and aminopeptidase N. Markers of proliferation such as perinuclear cytoplasmic activity (PNCA), Ki – 67, tritiated thymidine uptake, and ornithine decarboxylase may be useful as well.
Summary of Evidence by National Cancer Institute
There is fair evidence that screening would result in no (or minimal) decrease in mortality from esophageal cancer in the U.S. population. There is good evidence that screening would result in uncommon but serious side effects associated with endoscopy which may include perforation, cardiopulmonary events and aspiration, and bleeding requiring hospitalization. Potential psychological harms may occur in those identified as having Barrett’s esophagus who may consider themselves to be ill even though their risk of developing cancer is low.

Screening for Hepatocellular Cancer
Hepatocellular cancer (HCC) is the fourth most common cancer in the world. There is a distinct male preponderance among all ethnic groups in the United States, although this trend is most marked among Chinese Americans in whom the annualized rate of HCC among men is 26.7 per 100,000 and among women 6.2 per 100,000 population. Chronic hepatitis B and C are recognized as the major factors worldwide increasing the risk of HCC. Cirrhosis is also a risk factor for HCC, irrespective of the etiology of the cirrhosis. The annual risk of developing HCC among persons with cirrhosis is between 1% and 6%. Other risk factors include alcoholic cirrhosis, hemochromatosis, alpha-1-antitrypsin deficiency, glycogen storage disease, porphyria cutanea tarda, tyrosinemia, and Wilson’s disease.

The logic for screening for hepatocellular carcinoma (HCC) is based on the hypothesis that populations at high risk for HCC, such as those with cirrhosis, can be identified. However, 20% to 50% of patients presenting with HCC have previously undiagnosed cirrhosis. These patients would not be recruited into a surveillance program if the presence of cirrhosis is used to define a target population. The modalities potentially available for screening include serum alpha-fetoprotein (AFP) and ultrasonography.

Alpha-Fetoprotein (AFP)
Varying sensitivity of AFP for detecting HCC in both HBV-positive and HBV-negative populations has been reported which is attributable to overlap between screening and diagnosis study designs. When high risk populations have been screened, a sensitivity of 39% to 97%, specificity of 76% to 95%, and a positive predictive value of 9% to 32% have been reported. Titers of AFP also rise in acute or chronic hepatitis, pregnancy, and in the presence of germ cell tumors.

A prospective 16-year population-based observational study of screening for hepatocellular cancer among 1,487 Alaska Natives chronically infected with hepatitis B virus compared survival among screen-detected HCCs with an historical comparison group of clinically-diagnosed HCC. The screening program determined AFP levels every 6 months. It achieved 97% sensitivity and 95% specificity (excluding pregnant women) for HCC. These results have not been reproduced for other high risk groups, such as individuals with cirrhosis. Whether screening actually improved survival is not clear. Lead time bias, length bias and/or overdiagnosis of HCC (detection of tumors that will not affect morbidity or mortality) may wholly or partially account for the improved 5- and 10-year survival rates reported.

Hepatic Ultrasound
Studies in both healthy hepatitis B surface antigen carriers and in patients with cirrhosis have defined the performance characteristics of ultrasound as a screening test for HCC. Sensitivity in the former was 71% and in the latter 78%, with 93% specificity. The positive predictive values were 14% and 73%, respectively.

Computed Tomography
Studies in patients with cirrhosis suggest that CT may be a more sensitive test for HCC than ultrasound or AFP > 20.
Efficacy of Screening and Surveillance Programs
No randomized controlled trial of screening/surveillance (by AFP, US, CT) in patients at high risk for HCC, with disease-specific or all-cause mortality as the end-points, has been published. Limitations to such a study would include the large sample size required and the absence of adequate treatment for patients with even small tumors in some high-risk areas due to inadequate medical resources. 18,25

Summary of Evidence by National Cancer Institute
There is insufficient evidence to establish that screening by alpha-fetoprotein and/or imaging techniques (such as CT or ultrasound) would result in a decrease in mortality from hepatocellular cancer (HCC).

Screening for Colorectal Cancer
Colorectal screening programs that are aimed at population of eligible subjects are a cost-effective means of reducing colorectal cancer incidence and mortality within a community.26
Endorsement of colorectal cancer screening by national guidelines has been available for many years 27-29, yet most eligible adults do not get screening.30 This is mainly because of a lack of resources.

Evidence Supporting Fibre-optic Sigmoidoscopy (FS) Screening
Case control and cohort studies
The strongest evidence to support the use of FS for large-scale colorectal cancer screening comes from case control and cohort studies.31-35 The Northern California Kaiser Permanente study 31 compared patients who were dying of colorectal cancer to age and sex matched controls. Screening with the rigid sigmoidoscope was associated with at least a 30% overall reduction in colorectal cancer related mortality. There was a nearly 70% reduction in mortality from cancers in the rectum and sigmoid colon, and no significant reduction in mortality from more proximal colorectal cancer. A 10 years interval between screens was suggested as the mortality benefit persisted uniformly over the entire 10 year period before the death of patients. Other case control studies have generally confirmed these results.
A recent cohort study of 24,744 men demonstrated a 40 % reduction in incidence of all colorectal cancer and a 60 % reduction of distal colorectal cancer associated with exposure to either FS or colonoscopy.35

Randomized Controlled Trials
A small, randomized, controlled trial (n = 799) of a strategy of FS with colonoscopy for all people with polyps was conducted in Telemark, Norway,36 with follow-up of over 13 years. Screening led to an 80% reduction of colorectal cancer incidence, but there was higher overall mortality among screened subjects, because of an excess of cardiovascular death. Identification of causes for the excess deaths was limited by the lack of risk factor information on controls. Two large, randomized trails are currently under way, the Prostate, Lung, Colon and Ovarian (PLCO) cancer screening trials in the United States 37 and the FlexiScope trails in the United Kingdom.38 The PLCO trial will evaluate a program of FS performed every 5 years compared with no active screening and the UK trial will compare a single screening FS with no screening.

Indirect Evidence
Fecal Occult Blood Test Trials
Three randomized, controlled trials of fecal occult blood test (FOBT) have demonstrated a reduction in colorectal cancer – related mortality, with either annual or biennial rehydrated or nonrehydrated, guaiac – based, fecal occult blood tests 39-42. The end common pathway of FOBT screening is colonoscopy and removal of neoplastic lesions. If the procedure can be performed safely and with high participation
rates, any endoscopic screening program will reduce colorectal cancer incidence and cancer-related mortality. An endoscopic screening program that uses FS will be effective for reducing cancer incidence and mortality for the area of the colon within its reach. The screening is made more effective through the detection of advanced proximal neoplasia by way of a distal marker lesion prompting a total colonic examination with colonoscopy.

Flexible Sigmoidoscopy Plus Fecal Occult Blood Test

Theoretical Benefit and Theoretical Concern

Theoretically, the use of FOBT with FS should be more effective than either test used alone. The flexible sigmoidoscope is sensitive for the area of the colon within its reach. Although the FOBT is relatively insensitive in a single application, its sensitivity is roughly equivalent over the whole length of the colon. This helps in the detection of a small proportion of proximal neoplasia that would otherwise be missed by FS.

The major concern about the use of two tests in combination is the added complexity of the combined strategy, and the effect this may have on available screening resources and overall participation with screening.

Two recent trials documented that when FS is performed in addition to FOBT, the diagnostic yield for advanced lesions is significantly higher than for FOBT alone \(^{43,44}\). The decrease in colorectal cancer through combined use of these modalities needs to be proved.

Comparing single application of an FOBT or FS alone, FS detects more advanced neoplasms, even though compliance is often lower with FS.\(^{43,44}\) This would suggest that if one was going to do only one test, FS has a higher value. If both tests are to be done, then the FOBT should be done first, because a positive FOBT will prompt a colonoscopy, and the patients will only need to undergo a single procedure. An additional benefit of adding FOBT to FS is the possibility that the FOBT done during the interval between screens decrease the likelihood of developing symptomatic colorectal cancer between scheduled screening examinations.

Flexible Sigmoidoscopy Versus Colonoscopy for Average Risk Adults

The decision to perform a screening colonoscopy in place of a screening FS will need to be individualized, based on available resources, patient preferences, and risk factors for colorectal cancer. The major trade off is the added detection of proximal colorectal neoplasms when compared with the added risk of complications and the added cost of colonoscopy. The exact magnitude of these competing forces is not well-known.

Efficacy of Screening Colonoscopy

Increased Sensitivity for Colonic Neoplasia

Two cross-sectional, screening colonoscopy studies have shown increased sensitivity compared with a surrogate for FS (defined as the distal 30 to 60 cm of the colonoscopic examination) in the detection of advanced neoplasia.\(^{45,46}\) These studies noted that advanced proximal neoplasia in absence of a distal adenoma was present in 1.5 % to 4.0 % of asymptomatic, average risk, screens over 50 years old. One needs to remember that not all advanced adenomas will become cancer and the removal of adenomas is the chief cause of the morbidity of colonoscopy. Also, many patients with cancers will die of some other disease. These issues do leave a doubt about the overall benefit of colonoscopy as compared to what is inferred from the cross-sectional colonoscopy data.

Based on the available data, FS would detect 67 % to 80 % of the advanced adenomas found on colonoscopy, and correctly measure the overall colorectal cancer risk in more than 96 % of the
average-risk patients who are screened. If colonoscopy is used then 1000 patients would have to be exposed to the morbidity and mortality risks of colonoscopy to find 15 to 40 additional patients with proximal advanced adenomas. Only one to three additional cases of colorectal cancer per 1000 screened by FS would be expected, assuming a progression rate to cancer for advanced adenomas of 8\% by 10 years.\textsuperscript{47} This would result in an estimated zero to two death caused by proximal colorectal cancer. If FOBT screening were to be added to FS, an additional 5\% to 10\% of advanced adenomas and cancers might be detected per year of screening. This evidence suggested that the combined strategy of screening with FS plus annual FOBT would detected almost 90\% of advanced neoplasia in the presymptomatic phase, and at much less cost than primary screening with colonoscopy.

**Interval Between Screening Exams**

Most guidelines recommend screening with FS every 5 years or colonoscopy every 10 years.\textsuperscript{48-50} Case control studies of rigid sigmoidoscopy demonstrated equivalent effectiveness of sigmoidoscopy at reducing colorectal cancer-related morality over a 10-year interval.\textsuperscript{51} Follow-up after screening colonoscopy showed significant neoplasms to be rare 5 years after a negative colonoscopy.\textsuperscript{52} In addition, follow-up studies in patients with small polyps at sigmoidoscopy showed that the incidence of subsequent colorectal cancer is less than the general population; this suggested that prolonged follow-up after a negative exam may be justified.\textsuperscript{53}

**Statement of National Cancer Institute**

**Fecal Occult Blood Testing**

Guaiac-based fecal occult blood testing either annually or biennially using rehydrated or nonrehydrated stool specimens in people age 50 to 80 decreases mortality from colorectal cancer. (Level of evidence: 1) Potential harms include false-positive and false-negative results, and uncommon but serious complications, including colonic perforation resulting in sepsis, need for surgical repair procedures, or death associated with colonoscopy used to follow up a positive occult blood test result. Hemorrhage resulting from colonoscopic polypectomy may require blood transfusion, hospitalization, or surgical intervention.

**Sigmoidoscopy**

Regular screening by sigmoidoscopy in people over the age of 50 may decrease mortality from colorectal cancer. There is insufficient evidence to determine the optimal interval for such screening.

**References**


