Chapter 6

Colorectal Cancer

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INTRODUCTION

Adenocarcinoma of the colon and rectum (colorectal cancer, CRC) is the third most common cancer, the fourth most common cause of cancer death, and the second most common cancer in terms of the number of individuals living with cancer five years after diagnosis worldwide. An estimated 1,361,000 people are diagnosed with CRC annually; approximately 694,000 people die from CRC annually; and 3,544,000 individuals are living with CRC (Ferlay and others 2013).

Randomized controlled trials (RCT) have shown that screening is associated with a reduction in CRC mortality; in several high-income countries (HICs), organized, population-based screening programs have been introduced, starting in 2006. Some screening tests detect cancer at an early stage when treatment is less arduous and more often results in cure. Other screening tests have the ability to detect adenomas as well as cancer. Screening provides the opportunity to identify and remove adenomas and thereby to prevent the development of the disease (Lieberman and others 2012).

In general, the burden of disease, as measured by incidence and mortality rates, tracks the World Bank grouping of countries into low-, lower-middle, upper-middle, and high-income: the lowest-income countries have the lowest burden of disease. The ability to intervene to introduce screening and offer access to high-quality treatment is a function of resource availability, which is associated with income level. The ability of countries to develop interventions increases with income, suggesting a progression in policy options as country income increases.

The focus of this chapter is on those who are at average risk for CRC. In our discussion of policy options, we use a slightly different typology than income for resource availability, following chapter 3 in this volume (Anderson and others 2015). The resources available at a health facility can be described as basic, limited, enhanced, and maximal. The basic level corresponds approximately to the situation in low-income countries (LICs), the limited level to the situation in rural areas of lower-middle-income countries and upper-middle-income countries, the enhanced level to the situation in urban areas of lower-middle-income and upper-middle-income countries, and the maximal level to the situation in HICs. We provide suggestions for appropriate screening and treatment strategies that correspond to these resource levels for policy makers to consider.

BURDEN AND EPIDEMIOLOGY[1]

CRC is the third most common cancer in men (746,000 cases, 10.0 percent of all cancers in men worldwide); it is the second most common cancer in women (614,000 cases, 9.2 percent of all cancers in women worldwide). CRC incidence rates vary approximately tenfold in both genders worldwide and are higher in men than in women; the overall sex ratio of the age-standardized

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rates is 1.44:1 (Ferlay and others 2013). CRC incidence and mortality rates vary widely across regions, with mortality highest among men in HICs (map 6.1). The distribution of incidence in men and women and mortality in women may be seen in online annex 6A (maps 6A.1, 6A.2, and 6A.3). Approximately 55 percent of persons diagnosed with CRC are in HICs. Australia, Canada, New Zealand, the United States, and Western Europe have the highest estimated incidence rates, while incidence rates are intermediate in Latin America and the Caribbean. The lowest rates are in Sub-Saharan Africa, with the exception of southern Africa, and South Asia.

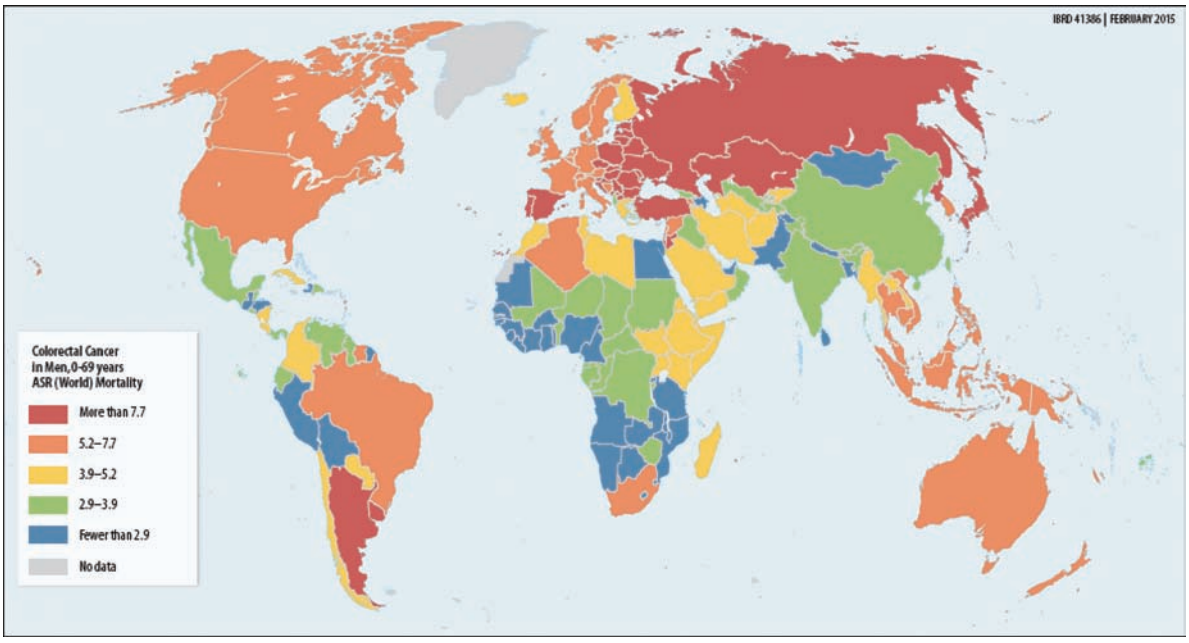
CRC mortality rates are lower in women than in men. However, compared with incidence rates, variability in mortality rates worldwide is less (sixfold in men, fourfold in women). Estimated CRC mortality rates are highest in Eastern and Central Europe (20.3 per 100,000 for men and 11.7 per 100,000 for women); Western Africa has the lowest estimated mortality rates (3.5 and 3.0, respectively).

Temporal Trends in Incidence and Mortality

Temporal trends in CRC incidence and mortality in a population reflect changes in the prevalence of risk factors in the population, coupled with changes associated with the introduction of screening. CRC incidence rates have stabilized or are declining in many HICs. Initially, the stabilization or decline may have been caused by declines in some risks, such as smoking; more recently, the change is likely to be caused by increased screening. Data from the Surveillance, Epidemiology, and End Results (SEER) Program for the state of Connecticut, United States, from 1940 to 2009, is one of the longest consistent time-series available. Incidence rates increased rapidly until the 1980s and then declined. (See online annex 6A, figure 6A.1). The peak in the 1980s represents the introduction of screening (primarily with fecal occult blood tests) and is consistent with an initial increase in incidence with screening because of detection of early-stage and preclinical disease. The decline post-1985 likely represents the impact of screening, as well as a decrease in risk factors such as smoking. The inverted U-shaped curve is more pronounced for men than for women (figure 6A.1). CRC incidence rates are now declining to the lowest level since the 1940s (Edwards and others 2010).

Trends for the United States as a whole are similar to those for Connecticut, but data are not available as far back as 1940 in a continuous series. A declining trend in CRC mortality is also seen in other HICs, including Australia, Denmark, and Japan. Incidence has not yet begun to decline in these three countries, likely because

Map 6.1 Global Colorectal Cancer Mortality in Men, 2012



Source: Based on data from Ferlay and others 2013.
Note: ASR = Age-Standardized Rate.

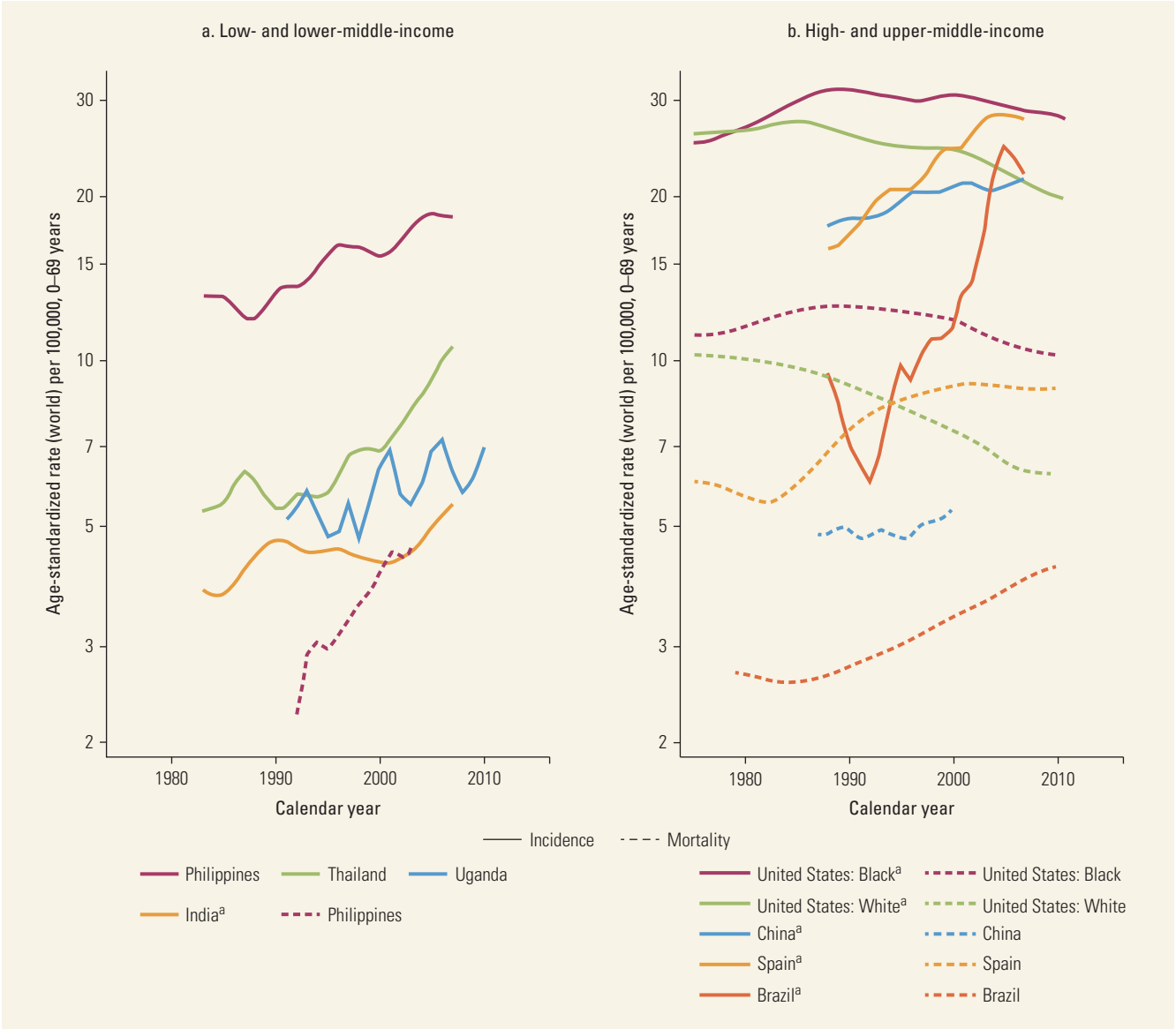
a "bulge" in reported cases occurs as CRC is detected at increasingly earlier stages. One would eventually expect to see incidence rates decline as in the United States, once a steady state is reached in screening.

The increase in CRC incidence and mortality in middle-income countries (MICs), such as Brazil, China, the Philippines, and Thailand (figures 6.1 and 6.2), is occurring prior to the onset of organized screening. Even in lower-middle-income countries such as India, incidence rates are increasing. Data from LICs are sparse, because of the limited availability and coverage of cancer registries.

Incidence and Mortality by Income Group

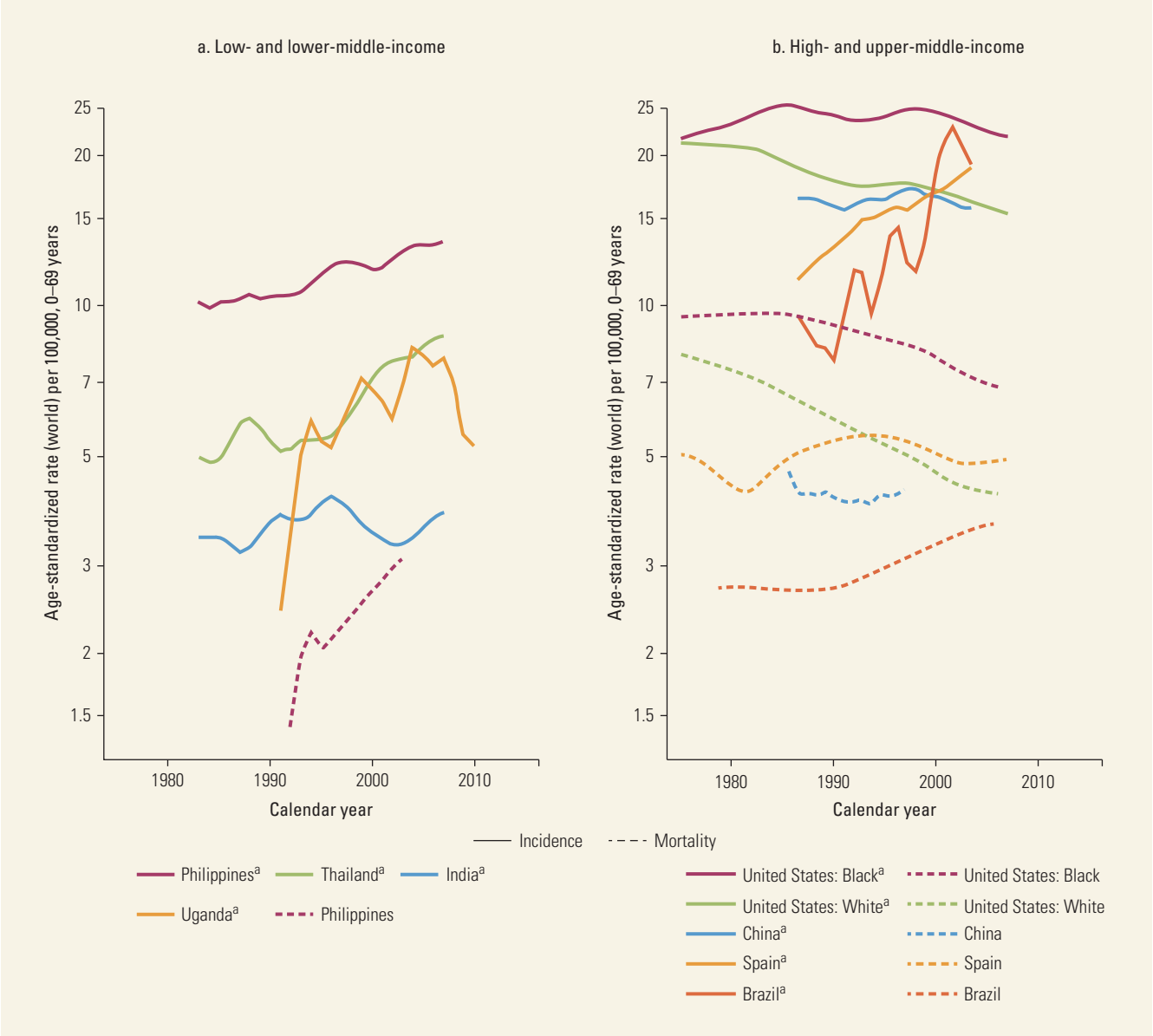
We classified the age-adjusted incidence and mortality rates for CRC by World Bank groupings of countries into LICs, lower-middle-income countries, upper-middle-income countries, and HICs (figure 6.3). The CRC

Figure 6.1 Trends in Age-Standardized Incidence and Mortality Rates of Colorectal Cancer in Men, Selected Countries, 1980–2010



Source: CI5 Plus (http://ci5.iarc.fr/CI5plus/Default.aspx) and WHO Mortality Database (http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html).
Note: Mortality data are not available for all economies shown. Incidence estimated from selected population-based cancer registries of consistently high quality (included in successive volumes of *Cancer Incidence in Five Continents*). Incidence data for the economies in the graphs are for Brazil (Goiania), China (Hong Kong SAR and Shanghai), India (Chennai and Mumbai), Philippines (Manila), Spain (Granada, Murcia, Navarra, and Tarragona), Thailand (Chiang Mai), Uganda (Kampala), United States (SEER).
a. Denotes rates based on an aggregate of one or more regional registries, as indicated.

Figure 6.2 Trends in Age-Standardized Incidence and Mortality of Colorectal Cancer Rates in Women, Selected Countries, 1980–2010



Source: CI5 Plus (http://ci5.iarc.fr/CI5plus/Default.aspx) and WHO Mortality Database (http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html).
Note: Mortality data are not available for all economies shown. Incidence estimated from selected population-based cancer registries of consistently high quality (included in successive volumes of *Cancer Incidence in Five Continents*). Incidence data for the economies in the graphs are for Brazil (Goiania), China (Hong Kong SAR and Shanghai), India (Chennai and Mumbai), Philippines (Manila), Spain (Granada, Murcia, Navarra, and Tarragona), Thailand (Chiang Mai), Uganda (Kampala), United States (SEER).
a. Denotes rates based on an aggregate of one or more regional registries, as indicated.

incidence and mortality rates increase with increasing country income, as indicated by the World Bank income groupings.

We derived the mortality-to-incidence ratio as an approximation of the CRC-specific mortality rate using the data from figure 6.3. The mortality-to-incidence ratio roughly represents the percentage of people with CRC who die of this disease. Although the low-income countries had the lowest CRC incidence and mortality rates, approximately 67 percent of men and 68 percent of women who develop CRC die from the disease. This is in strong contrast to the experience in HICs, where the incidence and mortality rates are much higher, but only approximately 31 percent of men and 30 percent of women with CRC die of this cancer. The corresponding figures for lower-middle-income countries

are 60 percent of men and 58 percent of women; for upper-middle-income countries, they are 49 percent of men and 47 percent of women. These results indicate that better survival is associated with higher country income. For China, the mortality-to-incidence ratio is 37 percent for men and 36 percent for women who develop CRC, whereas for India, the mortality-to-incidence ratio is 70 percent for men and 68 percent for women, indicating a very high case fatality rate from CRC in India.

In summary, the current burden of disease parallels the World Bank income groupings, with the lowest-income countries having the lowest burden of disease and poorest disease-specific survival.

Risk Factors

Age, sex, and family history are independent risk factors for CRC. The incidence of CRC increases with age, with approximately 7 percent of cases occurring in those younger than 50 years. The risk is somewhat higher among men than women. About 75 percent of new cases of CRC occur in those with no known predisposing factors. Those at increased risk because of a family history of CRC but without an identifiable genetic syndrome account for 15–20 percent of cases. HNPCC (Lynch syndrome) accounts for about 5 percent of cases, and familial adenomatous polyposis (FAP) accounts for about 1 percent (Winawer and others 1997). HNPCC and FAP are genetic polyposis syndromes. Those with a family history of CRC in a parent, sibling, or child are at a twofold increased risk of the disease (Butterworth, Higgins, and Pharoah 2006; Johnson and others 2013).

In terms of modifiable risk factors, epidemiological evidence supports roles for diet, lifestyle, and medications (Chan and Giovannucci 2010). In general, diets high in red meat are associated with an increased risk. For red meat, a recent meta-analysis reported a relative risk of 1.13 for consumption of five versus no servings per week (Johnson and others 2013). In addition, smoking, obesity, and a sedentary lifestyle are associated with an increased risk. For smoking, a relative risk of 1.26 for a 30-pack per year smoker versus a non-smoker, and for obesity, a relative risk of 1.10 for body mass index greater than 30 versus 22 kg/m^2 were recently reported (Johnson and others 2013). Calcium supplements may be associated with a modest reduction in risk. Aspirin and nonsteroidal anti-inflammatory drugs and postmenopausal hormone therapy among women are inversely associated with CRC risk, although the magnitudes of these effects are uncertain. The rise in CRC incidence rates in low- and middle-income countries (LMICs) is largely attributed to the adoption of Western diets and sedentary lifestyles.

Figure 6.3 Age-Standardized Incidence and Mortality Rates of Colorectal Cancer by World Bank Income Classification, 2012

Source: Ferlay and others 2013.

INTERVENTIONS

Screening

CRC Screening Tests

Guaiac Fecal Occult Blood Test (gFOBT) gFOBT is a stool test that indirectly detects blood in the stool that may be caused by bleeding from CRC. A positive test is not specific for the presence of human blood; however, it may reflect blood from ingested animal meats, for example. gFOBT is supported by evidence from RCTs with long-term follow-up and CRC mortality as the outcome. RCTs of periodic (annual or biennial) gFOBT show a reduction in mortality from CRC of 13 to 33 percent, with up to 50 percent compliance with periodic gFOBT (Hardcastle and others 1996; Kronborg and others 1996; Mandel and others 1993; Towler and others 1998). Individuals with a positive gFOBT must be followed up by colonoscopy.

Fecal Immunochemical Test (FIT) FIT is a stool test that uses an antibody against human globin, the protein part of hemoglobin. A positive FIT is specific for human blood. There are no large-scale RCTs that have evaluated FIT with long-term follow-up and CRC mortality as the outcome, although two RCTs are underway. FIT is supported by RCTs of FIT versus gFOBT (van Rossum and others 2008) and FIT versus colonoscopy (Quintero and others 2012). These are cross-sectional RCTs with cancer detection and advanced adenoma as the outcomes. The RCT of FIT compared with gFOBT shows that the use of FIT is associated with higher adherence/compliance rates than the use of gFOBT, and

also that FIT is superior to gFOBT in detection rates and positive predictive values for adenomas and cancer (van Rossum and others 2008). The RCT of FIT compared with colonoscopy showed higher participation in the FIT group than in the colonoscopy group, and that the numbers of subjects in whom CRC was detected were similar in the two groups, but a greater number of subjects with adenomas were identified in the colonoscopy group (Quintero and others 2012).

Flexible Sigmoidoscopy (FS) FS is an endoscopic procedure in which a flexible fiberoptic instrument is used to examine the rectum and lower (distal) colon, unlike colonoscopy, which examines the rectum and total (upper and lower) colon. Cancers and precancerous lesions, such as adenomas observed in this area, can be removed or biopsied. Large-scale RCTs of FS, coupled with colonoscopy for those who test positive, have shown reductions in CRC incidence (Atkin and others 2010; Schoen and others 2012; Segnan and others 2011) and CRC mortality (Atkin and others 2010; Schoen and others 2012) over a 10-year period. A meta-analysis of the results from the published RCTs of FS screening reported, in an intention-to-treat analysis, an 18 percent reduction in relative risk of CRC incidence and a 28 percent reduction in CRC mortality (Elmunzer and others 2012).

Colonoscopy Colonoscopy is an examination of the entire colon and rectum with a flexible fiberoptic endoscope. Colonoscopy detects asymptomatic cancers, and precancerous lesions can be removed. Evidence from the National Polyp Study, analyzed as an observational cohort study, indicates that colonoscopy with polypectomy is associated with a reduction in CRC incidence and mortality (Winawer and others 1993; Zauber and others 2012). No published evidence from RCTs has evaluated screening colonoscopy with long-term follow-up and CRC mortality as the outcome. However, indirect evidence to support screening colonoscopy comes from RCTs of gFOBT, in which persons with a positive gFOBT underwent colonoscopy. In these trials, colonoscopy with polypectomy was responsible for the mortality reduction associated with gFOBT screening. Further indirect evidence comes from RCTs of FS screening, which demonstrate a reduction in CRC mortality. By extrapolation, it would be expected that since colonoscopy evaluates the entire colon, screening colonoscopy would be associated with a reduction in CRC mortality that might exceed that observed for screening FS. Several large-scale RCTs of colonoscopy are underway, with CRC mortality as the primary outcome. In the NordICC trial in Europe, screening colonoscopy is being compared with usual care. In the COLONPREV trial in Spain and the CONFIRM trial by the U.S. Department of Veterans Affairs, colonoscopy is being compared with FIT.

Fecal DNA A cross-sectional study comparing the performance of a stool DNA prototype versus gFOBT versus colonoscopy reported that the stool DNA test detected a greater proportion of CRCs and CRCs plus adenomas with high-grade dysplasia than the gFOBT, 51.6 percent vs. 12.9 percent, and 40.8 percent vs. 14.1 percent, respectively (Imperiale and others 2004). However, the majority of neoplastic lesions was not detected by either test. Since then, stool DNA technology has continued to evolve (Ahlquist and others 2012). A large-scale, cross-sectional study (DeeP-C) of a next-generation stool DNA test has recently been published (Imperiale and others 2014) and indicates 92.3 percent sensitivity for the detection of CRC and 42.4 percent sensitivity for the detection of advanced adenomas.

Computed Tomographic Colonography (CTC) CTC is a computerized tomography examination of the abdomen and pelvis in which imaging information, when processed with special imaging software, provides images of the colon and rectum. Images are also produced of structures outside the colon (extracolonic findings). The technique requires bowel preparation and colonic insufflation, but not conscious sedation, as is generally required for colonoscopy. CTC does not permit biopsy or polyp removal; colonoscopy is required. The two largest reports evaluating CTC in asymptomatic persons are cross-sectional studies that compared CTC and colonoscopy for the detection of adenomas (Johnson and others 2008; Pickhardt and others 2003). Taken together, these studies found that CTC was comparable to colonoscopy for detecting adenomas ≥ 10 mm (pooled sensitivity was 92 percent), but fell short in detecting smaller adenomas (6–9 mm).

Role of Colonoscopy in Diagnosis and Surveillance

Having adequate colonoscopy resources is a key aspect in implementing CRC screening, because of the role of colonoscopy in diagnosis and surveillance. When a less invasive screening test—such as gFOBT, FIT, or FS—is used, colonoscopy is required to investigate those with a positive (abnormal) screen, and it is the final common pathway to establish a diagnosis. Colonoscopy is also recommended for surveillance, depending on the findings at the initial colonoscopy, which are used to stratify risk for subsequent colorectal neoplasia.

Guidelines for Colonoscopic Surveillance In 2012, the U.S. Multi-Society Task Force on CRC/American Cancer Society (USMSTF) published updated surveillance guidelines that take into account the serrated neoplasia pathway (Lieberman and others 2012). Based on the findings at the baseline colonoscopy, the recommended surveillance intervals are as follows: 10 years for those with no polyps or small (< 10 mm) hyperplastic polyps in the rectum or sigmoid; 5–10 years for those with 1 or 2 small (< 10 mm) tubular adenomas; three years for those with three to 10 tubular adenomas, one or more tubular adenomas ≥ 10 mm, one or more villous adenomas, or an adenoma with high-grade dysplasia; and less than three years for those with more than 10 adenomas. When serrated lesions are detected at the baseline colonoscopy, the recommended surveillance intervals are as follows: five years for those with sessile serrated polyps (SSPs) < 10 mm with no dysplasia, three years for SSPs ≥ 10 mm or SSPs with dysplasia or a traditional serrated adenoma, and one year for those with serrated polyposis syndrome.

Colonoscopy Effectiveness in Usual Practice

Large-scale, population-based studies have shown that lesions can be missed at colonoscopy, including adenomas and cancers (Baxter and others 2009; Bressler and others 2007). It is often not possible to be certain that a CRC that was not detected at the time of colonoscopy, but subsequently diagnosed, was a missed cancer. The alternative explanation is that the "new" cancer was not present at the time of the colonoscopy, but arose and grew rapidly following the procedure. These new or missed cancers have been referred to as postcolonoscopy CRCs (Rabeneck and Paszat 2010) or interval cancers.

Evidence from population-based, case-control studies shows that colonoscopy is associated with a reduction in overall CRC mortality; however, the magnitude of the effect is less in the proximal colon (Baxter and others 2009; Brenner and others 2011). This means that in usual practice, colonoscopy is less effective in the proximal colon. This finding is attributed to suboptimal colonoscopy quality or differences in tumor biology between those cancers that arise in the proximal compared with the distal colon. These findings have given rise to renewed emphasis on the critical importance of colonoscopy quality and increased attention to CRC carcinogenesis. In particular, the recognition that lesions arising in the serrated neoplasia pathway have been underdetected at colonoscopy may explain, in part, the lesser effectiveness of colonoscopy in the proximal (right) colon.

What are the possible reasons for postcolonoscopy CRCs?

- First, the lesion may not have been seen because the cecum was not reached during the procedure (reaching the cecum is more challenging technically than reaching the distal colon); the bowel preparation was not adequate and the mucosa was not fully visualized (the upper or proximal colon is more difficult to clean); or the technique was inadequate, that is, the lesion was simply not seen.
- Second, a prior polypectomy may have been incomplete. Polypectomy is the key to reducing CRC incidence following colonoscopy.
- Third, a rapidly progressing CRC may not have been present at the initial colonoscopy, which may have been truly negative.

What all of this means is that colonoscopy fails to detect a small but clinically important percentage of lesions, and this lack of effectiveness is more pronounced in the right colon, making meticulous technique paramount.

CRC Screening Guidelines

International Agency for Research on Cancer In 2010, the International Agency for Research on Cancer (IARC), an agency of the World Health Organization (WHO), published a landmark document, *European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis* (Segnan, Patnick, and von Karsa 2010). The recommendations are based on a comprehensive and systematic review of the scientific evidence and are intended for organized screening programs (see below). The guidelines recommended annual or biennial screening with gFOBT, FIT screening at an interval not to exceed three years and at a minimum to include screening for those ages 60–64 years, and FS screening at an interval not less than 10 years, with the best age range for screening between ages 55 and 64 years but not exceeding age 74 years. Colonoscopy was not recommended for CRC screening in the European Union.

U.S. Preventive Services Task Force (USPSTF) USPSTF recommends routine screening for average risk persons ages 50–75 years, no routine screening for persons ages 76–85 years, and no screening for persons older than age 85 years (USPSTF 2008). USPSTF recommends annual screening with high-sensitivity gFOBT, or FS every five years with high-sensitivity gFOBT every three years, or colonoscopy every 10 years. USPSTF did not assess barium enema because of lack of evidence and declining

use, and it concluded that the evidence was insufficient to assess the benefits and harms of CTC and fecal DNA for CRC screening.

U.S. Multi-Society Task Force/American Cancer Society (USMSTF) USMSTF defines two categories of screening test (Levin and others 2008). In the first category are tests that primarily detect cancers. Tests that are recommended in this category for screening persons at average risk (age 50 years and older, no symptoms, no family history of the disease) are the following: annual high-sensitivity gFOBT, annual FIT, or stool DNA (interval uncertain). In the second category are tests that detect cancers and adenomas. Recommended tests in this category for screening persons at average risk are: FS every five years, colonoscopy every 10 years, double-contrast barium enema every five years, or CTC every five years.

Organized Versus Opportunistic Screening

Screening is not simply a test; it is a process. Chapter 12, this volume, discusses organized and opportunistic screening in detail. Compared with opportunistic screening, organized screening focuses much greater attention on the quality of the screening process, including follow-up of participants (Miles and others 2004). Thus, a key advantage of organized screening is that it provides greater protection against the possible harms of screening. Poor follow-up of those who test positive may occur, for example, when those with a positive (abnormal) FIT fail to undergo colonoscopy, the recommended next step in the screening process (Miles and others 2004).

Organized CRC Screening Worldwide The International Colorectal Cancer Screening Network (ICRCSN) is a consortium of organized initiatives delivering screening to their populations. In 2008, ICRCSN conducted a survey of full or pilot programs that fulfill at least four of the IARC criteria for an organized screening program (Benson and others 2012). At that time, 43 organized screening programs were identified, of which 35 programs had been collecting data for at least 12 months and were eligible for the survey. Of the 35 programs from 24 countries, 26 were full programs and nine were pilot programs. The majority of the programs were in Europe, with a few from North America, South America, and the Western Pacific. The majority (28) used stool-based tests as their primary screening test: 16 used gFOBT, nine used the FIT, and three used both tests. Wide variations were observed in the ability of the jurisdictions to report on performance indicators, such as the participation rate, the gFOBT or FIT positivity rate, and the cancer detection rate.

Performance of Organized Screening Programs In general, a period of at least 10 years is required to plan, pilot, and implement an organized CRC screening program (von Karsa and others 2010). The European Guidelines define key performance indicators for CRC screening, including participation, follow-up colonoscopy among those with a positive gFOBT, retention rates, cancer detection rates, and CRC mortality (von Karsa and others 2010). High performance in all of these measures is required in CRC screening programs. A few programs have published early results for participation. For example, Ontario launched its provincewide, organized screening program, ColonCancerCheck, in 2008. The program is based on gFOBT for those at average risk and colonoscopy for those at increased risk, defined by a family history of one or more first-degree relatives with the disease. The target population—men and women ages 50–74 years—is 3.4 million. Prior to launch of the program, gFOBT participation in 2003–04 was 15 percent; in 2010–11, gFOBT participation was 29.8 percent (Rabeneck and others 2014).

Some high-income Asian countries have begun to implement organized screening: Japan, the Republic of Korea, and Singapore. Currently, organized, population-based screening programs do not exist in the majority of LMICs. As MICs develop organized cancer screening programs, CRC screening is under consideration. There are or have been pilot studies of CRC screening conducted in several upper-middle-income countries and economies using gFOBT, including Thailand (Lampang province: http://www.iarc.fr/en/staffdirectory/display-staff.php?id=10114); Shanghai is embarking on a pilot study, as is Argentina (Manzur 2013). These pilot studies are important to lay the groundwork for national programs (Goss and others 2013).

Other countries offer opportunistic screening, largely restricted to the population covered by work-based health insurance. As a high-income economy, Taiwan, China, offers free screening under the national health insurance program (Ng and Wong 2013). Formal sector employees and/or government employees in much of Latin America and the Caribbean are covered for cancer screening. However, most MICs do not have organized screening programs.

International Efforts to Advance CRC Screening: IARC The vision of the Early Detection and Prevention (EDP) Section of the IARC is to serve as the major global resource for high-quality scientific and evidence-based information on cancer prevention and early detection interventions. The EDP Section evaluates and reports

on interventions for early detection and prevention. The findings guide the development of public health policy, with a particular focus on cancer control in LMICs. The EDP Section's work catalyzes the implementation of CRC prevention and early detection programs that follow the principles of organized screening as outlined, to the extent feasible.

Experience from the European Union shows that a minimum period of 10 years is required to establish a population-based cancer screening program, with any impact taking even longer (Lee and others 2013). Examples of early detection and prevention work include the *European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis* (Segnan, Patnick, and von Karsa 2010). In addition, a network of reference and training centers (European School of Screening Management) has been created that is developing and piloting training courses for planning, implementation, quality assurance, and evaluation of population-based cancer screening programs. The European School of Screening Management is intended to serve as a platform to connect and facilitate collaboration among relevant personnel from HICs and LMICs. Further, the EDP Section provides scientific and technical support to upper-middle-income countries, such as Albania and Belarus, to assist them in moving forward with population-based cancer screening programs.

Other International Organizations and Networks Promoting Screening The International Cancer Screening Network is a consortium of countries that have active population-based cancer screening programs and active efforts to evaluate and improve the processes and outcomes from cancer screening in practice. These programs can be national or subnational in scope, and established or pilot-based. Administered by the Applied Research Program of the U.S. National Cancer Institute, the consortium includes 33 countries and holds biennial meetings; specific activities are moved forward through working groups. Participation in the International Cancer Screening Network is open to any country that has initiated a population-based screening program.

The World Endoscopy Organization is a federation of national digestive endoscopy societies. Its mission includes the advancement of digestive endoscopy for the diagnosis and treatment of gastrointestinal diseases in underserved areas. The World Endoscopy Organization has an active CRC Screening Committee that holds annual meetings in the East Asia and Pacific region, Europe, and the United States, in conjunction with the major regional scientific meetings of gastroenterology societies. The meetings provide a forum to facilitate the presentation and discussion of new knowledge related to CRC screening and sharing of best practices across the world.

The International Digestive Cancer Alliance promotes the screening, early detection, and primary prevention of digestive cancers worldwide, including development of practice guidelines (http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/06_colorectal_cancer_screening.pdf). The International Digestive Cancer Alliance recommended staging the approach to screening, with respect to the choice of screening test, to the resources available in a given country (Winawer 2007).

Diagnosis

In HICs, persons with CRC can present in several ways:

- First, the cancer can be detected as a result of screening. When gFOBT, FIT, or FS is used as the initial screening test, colonoscopy is undertaken as a diagnostic test to evaluate those with an abnormal screening test. During the colonoscopy, polyps are removed and masses or other suspicious lesions are either removed or biopsied to establish a pathological diagnosis.
- Second, the cancer can be detected when an individual undergoes colonoscopy to evaluate large bowel symptoms, such as rectal bleeding, anemia, or a change in bowel habits.
- Third, some individuals may present as an emergency, such as a large bowel obstruction, in which case the cancer may be diagnosed at surgery without prior diagnostic evaluation.

Staging

When the cancer is diagnosed in nonemergency presentations, staging and complete visualization of the colon and rectum with colonoscopy are undertaken. Complete colonoscopy is also undertaken for the purpose of detecting synchronous cancers (present in 3–5 percent of cases); if not done prior to definitive treatment, it should be done within 6–12 months. Colonoscopy will also detect synchronous premalignant adenomas, which can be removed to reduce the risk of subsequent cancer. Barium enema, a radiological test, was used to diagnose CRC prior to the widespread availability of colonoscopy in HICs and may still be relevant in LMICs.

Clinical staging to determine the extent of disease focuses on imaging the liver and lungs, the two most common sites of spread. In HICs, computerized tomography is used to detect these distant metastases

(Leufkens and others 2011). Chest X-ray and abdominal ultrasound are less expensive alternative tests that can be used in lower-income settings.

Pathologic stage I refers to CRCs that are confined to the surface of the bowel. Stage II means the cancer has invaded through the muscle layer of the bowel wall. Stage III cancers involve the local lymph nodes. These stages are usually determined by examining the tumor pathologically after surgery. Stage IV cancers have spread (metastasized) into other organs.

Treatment

Surgery for Colon Cancer

The cornerstone of treatment is surgical resection. For early-stage cancers, surgery alone may cure the disease. For colon cancer, the preferred procedure is a hemicolectomy (resection of either the right or the left colon) with wide (> 5 cm) margins of normal colon. This procedure can typically be performed by a general surgeon. Where available, minimally invasive (laparoscopically-assisted) techniques have produced similar long-term results compared with an open procedure, but with shorter hospital stays and increased speed of recovery. Achieving these benefits requires an experienced surgeon and specialized instruments, however; even in HICs, the cost-effectiveness of this approach has been questioned. A minimum of 12 lymph nodes in the surgical specimen is required for adequate staging and is associated with better outcomes than a lesser dissection. In patients presenting with stage IV colon cancer where cure is not possible, if the primary (that is, the site of the original cancer) is not associated with symptoms and the metastatic disease (that is, the sites where the disease has spread) is anticipated to be controlled with chemotherapy, the primary tumor does not necessarily need to be resected.

Surgery for Rectal Cancer

Surgery for rectal cancer is much more complex. High-volume, specialized surgeons and centers have been associated with better outcomes: less likely to need an ostomy bag, lower rates of local recurrence, better overall survival.

- Mid-to-upper rectal tumors can be resected with a *low anterior resection*, which leaves the rectal sphincter intact, thereby avoiding colostomy.
- Lower-lying tumors, that is, those within 2–3 cm of the anal sphincter or levator muscles, require an *abdominal perineal resection* and creation of a permanent stoma requiring colostomy. Surgeon skill often determines how low a low anterior resection can be done.
- *Total meso-rectal excision*, the meticulous, sharp dissection of perirectal tissues with removal of the primary tumor and lymph nodes all in one piece, has been shown to decrease local relapse rates.
- To avoid a stoma, *transanal excision* of small, early-stage distal tumors with good prognostic features can be considered. (Good is defined here as T1N0, < 3 cm, < 30 percent circumference, not poorly differentiated, and no lymphovascular or perivascular invasion.)

Radiation

The availability of radiation therapy is most relevant for cancers of the rectum, as local recurrence is much more common than in colon cancer, because of the inability to obtain wide margins and the lack of a serosal barrier. Radiation therapy has improved local control for persons with stages II and III rectal cancer (Hoffe, Shridhar, and Biajioli 2010). Evidence suggests that compared with postoperative radiation, preoperative radiation is associated with improved surgical outcomes and disease-free survival (Sebag-Montefiore and others 2009). This decision depends on determining the stage of cancer preoperatively, which requires diagnostic services such as magnetic resonance imaging or specialized endorectal ultrasound capability. Where these are not available, postoperative delivery of radiation and chemotherapy still provides important benefits. In settings with access to radiation but difficulty obtaining or delivering chemotherapy, or where travel requirements preclude the 5.5 weeks of daily long-course radiotherapy, short-course radiotherapy may be a preferred option (Içli and others 2010).

Chemotherapy

Evidence-based practice guidelines recommend six months of adjuvant chemotherapy following surgery for persons with stage III colon cancer (Benson and others 2000) and stages II and III rectal cancer. FOLFOX (FOLinic acid [leucovorin], Fluorouracil, OXaliplatin) is the preferred regimen. If chemoradiotherapy is given for rectal cancer, only four months of chemotherapy are required. In addition to the cost of the drugs, however, systemic chemotherapy always requires the ability to monitor blood counts for safety and may require venous access devices.

Management of Metastatic Colorectal Cancer

Metastatic CRC is treated the same way, regardless of whether it started in the colon or rectum. Although metastatic disease is generally incurable, it is increasingly recognized that, where possible, in 10–20 percent of patients, aggressive resection of liver and lung metastases

may lead to cure 20–30 percent of the time. Such surgery requires highly specialized training and centers, even in HICs. Alternatives to surgical resection, such as *radiofrequency ablation* and *stereotactic body radiotherapy*, can provide long-term control in these situations, but surgical resection is preferred where feasible. Perioperative chemotherapy with FOLFOX has been shown to improve disease-free survival in this setting. For the majority of patients with metastatic CRC, however, treatment is palliative, with an expected median survival with surgery alone of 6–12 months.

International Partnerships for CRC Care

As with CRC screening, international partnership arrangements can support diagnosis and treatment in LMICs. The American Society of Clinical Oncology (http://www.asco.org) established an International Affairs Committee in 2007 with a goal of reducing disparities in cancer care and maximizing chances of survival through the global exchange of oncologic knowledge. The National Comprehensive Cancer Network (http://www.nccn.org) provides translations of many of its guidelines into other languages, such as Chinese, Japanese, and Spanish, and has published local adaptations of guidelines, for example, for countries in the Middle East and North Africa. One National Comprehensive Cancer Network institution, the MD Anderson Cancer Center at the University of Texas, lists 28 sister institutions, as well as affiliates in at least 18 countries, 10 of these in LMICs (http://www.mdanderson.org/education-and-research/education-and-training/schools-and-programs/global-academic-programs/sister-institutions/index.html). Similar partnerships exist with other major cancer centers.

COST-EFFECTIVENESS OF CRC SCREENING AND TREATMENT

A systematic search of the literature on CRC screening and treatment was undertaken using PubMed from 2004 to 2013 to identify relevant articles for LMICs, as well as selected high-income Asian countries and economies that can help serve as regional models, principally Hong Kong SAR, China; the Republic of Korea; Singapore; and Taiwan, China. The parameters were medical subject heading terms (colorectal neoplasms, colonic neoplasms, rectal neoplasms, CRC, colon cancer, or rectal cancer); colonoscopy or sigmoidoscopy; and multiple terms related to economic evaluation, cost, cost analysis, and cost-effectiveness.

This search was supplemented by a nonsystematic search using the Internet for certain LMICs. For HICs, a fairly recent publication, Greenberg and others (2010), was used. This is a systematic review of the cost-effectiveness literature for various cancers, primarily for industrialized countries, and has the advantage that all the costs have been standardized to those of a common year. For additional analyses, comparing the cost-effectiveness of CRC screening and treatment with screening and treatment for other cancers in LMICs, see chapter 16 in this volume (Horton and Gavreau 2015).

Screening

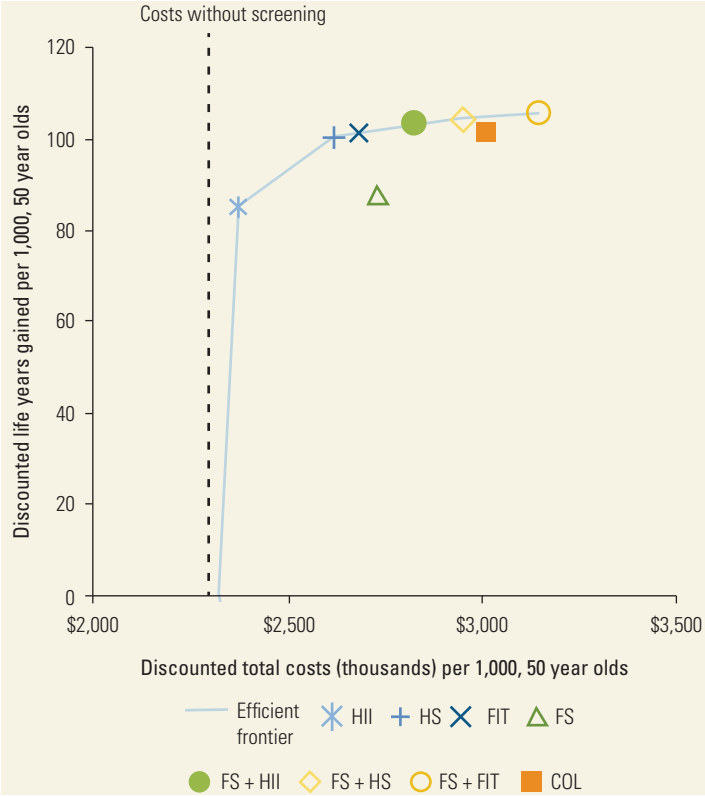
Cost-effectiveness studies for CRC screening in the United States, several European countries, and high-income Asian countries and economies (Hong Kong SAR, China; Korea; Singapore; and Taiwan, China) generally conclude that screening is cost-effective compared with no screening. The cost-effectiveness of several screening options can be considered. Guidelines generally recommend that screening should begin at age 50 years (except for those with strong family history of CRC), but it can stop at different ages (such as 70, 75, 80, or 85). Tests can be undertaken in combination, such as FS combined with a sensitive gFOBT. The use of an efficiency frontier for each individual country can help to identify the most appropriate screening strategy given the budget constraints (see figure 6.4 for the United States).

Studies in the United States

Cost-effectiveness studies in the United States generally have used one of a few large cancer microsimulation models. Comparative studies (for example, Pignone and others 2002 and Pignone, Russell, and Wagner 2005) suggest that results are sensitive to the parameters used, particularly cost. The models also entail different assumptions about disease progression that also affect relative test performance (Pignone, Russell, and Wagner 2005). Since the review by Pignone and others (2002), three microsimulation models for CRC have become part of the U.S. National Cancer Institute consortium for Cancer Intervention and Surveillance Modeling Network (CISNET), a consortium of National Cancer Institute-sponsored investigators that use statistical modeling to improve the understanding of cancer control interventions in prevention, screening, and treatment, and their effects on population trends in incidence and mortality. These models can be used to guide public health research and priorities.

Figure 6.4 shows the results for cost-effectiveness analysis from one CISNET model, the Microsimulation Screening Analysis model from Erasmus University Medical Center, for eight CRC screening strategies beginning at age 50 years. Figure 6.4 is a modification of

Figure 6.4 Discounted Costs and Discounted Life Years Gained for Eight Colorectal Cancer Screening Strategies and the Efficient Frontier



Source: Zauber 2010, based on Knudsen and others 2010.
Note: COL = colonoscopy; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; HII = Hemoccult II (fecal occult blood test, FOBT); HS = Hemoccult Sensa (FOBT). This analysis assumes 100 percent adherence with each strategy.

a larger analysis as given by Knudsen and others (2010), which assumed that subjects were 100 percent adherent to screening tests and subsequent diagnostic or treatment for those with positive tests or cancer diagnosis. Gains in life years are plotted on the y-axis and total costs are plotted on the x-axis. Each possible intervention strategy is represented by a point. The higher the point is, the more effective is the screening strategy; the further to the right the point is, the more expensive is the screening strategy (Marks 2002).

Cost-effectiveness analysis does not select which strategy is economically preferred overall, but only which strategy is the most effective in terms of life years gained for a given level of desired (or possible) expenditure. The eight CRC screening strategies are ranked in order of the procedure, with the least life years gained relative to no screening (Knudsen and others 2010). The strategies are then compared incrementally by ordering of the life years gained relative to the costs of each screening strategy. Those strategies that have the most life years gained for a given level of cost are considered to be on the efficiency frontier. In this example, the lowest-cost option of those options on the frontier is the less sensitive gFOBT (Hemoccult II). However, if the budget available for testing increases, then a more sensitive gFOBT (Hemoccult Sensa) or FIT is the next best choice for cost relative to life years gained with screening. The next choice would be FS with some type of fecal occult blood test (FOBT). Colonoscopy lies just below the efficient frontier, with the rankings for life years gained relative to costs similar to those of FS with gFOBT or FIT. The rankings using two other models (the SimCRC model from University of Minnesota and Massachusetts General Hospital, and the CRC-SPIN model from Group Health Research Institute; see http://cisnet.cancer.gov/profiles/) were broadly similar, although the absolute cost per life year gained differed between models. All of the strategies had average costs per life year gained (compared with no screening) well within the threshold considered cost-effective in the United States (below US$50,000 per life year gained).

Taken together, the results from the U.S. analyses using simulation models suggest the following:

- Screening is cost-effective; since compliance is not 100 percent, encouraging screening by any of a small group of strategies will save life years.
- Where the total budget available is limited, the lowest-cost testing strategy involves gFOBT.
- The differences in the cost-effectiveness of some strategies are modest and susceptible to variation in assumptions.
- Knowledge of details of disease progression is limited, for example, how untreated adenomas progress to cancer or how this progression varies by individual characteristics such as age, gender, and family history. Different assumptions regarding disease progression affect the results of the simulation model.

The evidence base for different screening methods continues to evolve. FS and colonoscopy can be performed by appropriately trained nonphysicians, including nurses (Maule 1994; Wallace and others 1999). Newer generations of chemotherapy agents increase life expectancy modestly, but they considerably increase treatment costs; accordingly, most screening methods (although not colonoscopy by a narrow margin) remain cost-saving (Lansdorp-Vogelaar and others 2009).

European Studies

The European studies identified by the systematic review by Pignone and others (2002) (two studies of gFOBT and one of FS, in Denmark, Norway, and the United Kingdom) all supported the conclusion that

screening is cost-effective compared with no screening, and the cost per life year saved was lower than in the United States because of the higher overall medical costs in the United States (Gyrd-Hansen, Søgaard, and Kronborg 1998; Norum 1998; Whynes and others 1998).

Studies in High-Income Economies in Asia

Table 6.1 summarizes cost-effectiveness results for four studies of Asian economies, with the standardized model for the United States from Pignone, Russell, and Wagner (2005) for comparison. The Asian economies are Hong Kong SAR, China; the Republic of Korea; Singapore; and Taiwan, China. Observations from these results include the following:

- Screening in the four Asian economies is cost-effective, although the simpler models used in some studies may underestimate costs.
- Relative costs of procedures such as colonoscopy/FS and colonoscopy/gFOBT vary by country, which is likely to affect rankings.
- For the Republic of Korea, for example, it has been argued that colonoscopy reimbursement rates are artificially low and do not reflect cost (Park, Yun, and Kwon 2005). This is likely to affect the relative ranking of strategies for that country.

These four Asian economies do not all have published cost-effectiveness thresholds used for public decision making. However, from the WHO Commission on Health (WHO 2001), health interventions costing up to three times per capita gross domestic product per disability-adjusted life year saved should be considered. By this criterion, all the methods of CRC screening considered here (gFOBT, FS, and colonoscopy) would be acceptable in these four economies. Another study for

Table 6.1 Selected Costs and Cost-Effectiveness of Screening, Per Capita GDP, and Colorectal Cancer Incidence in Four High-Income Asian Economies Compared with the United States

Item cost or value (US$)	United States 2005[a]	Korea, Rep. 2004[b]	Taiwan, China 2004[c]	Hong Kong SAR, China 2003[d]	Singapore 2004[e]
gFOBT	10	1.91	0.60	4	5.59
Colonoscopy (diagnostic)	625	43.80	66.20	450	368.72
Colonoscopy (polyp removal)	900	—	—	830	446.93
Sigmoidoscopy	200	22.18	35.30	244	134.08
Treat CRC, local	24,000	4,291.67	3,117.60	16,552	11,173.18
Treat CRC, regional	31,000	—	7,705.90	27,321	19,553.07
Treat CRC, distant	40,000	8,583.33	7,647.10	71,751	—
Colon perforation	24,000	2,500	1,617.60	10,790	4,863.69
Cost-effectiveness versus no screening US$/LYS	gFOBT 9,676 COL 21,000 (median of 5 models, standardized assumptions)	COL (5 years) 1,142; others dominated	gFOBT 70 FS 594 COL 407	gFOBT 6,222 FS 8,044 COL 7,211	gFOBT 91 FS 190 COL 225
Per capita GDP[f]	46,760	19,028	17,461	31,426	34,466
CRC incidence[g]/100,000 (age-standardized to world population)	34.1 men 25.0 women	46.9 men 25.6 women	40.2 men 29.7 women (Taiwan, China)	50.1 (crude, men and women combined)	34.1 men 25.0 women

Note: COL = colonoscopy; CRC = colorectal cancer; FS = flexible sigmoidoscopy; GDP = gross domestic product; gFOBT = guaiac fecal occult blood test; LYS = life years saved; — = not available.

a. Pignone, Russell, and Wagner 2005.
b. Park, Yun, and Kwon 2005.
c. Wu and others 2006.
d. Tsoi and others 2008.
e. Wong, Leong, and Leong 2004.
f. World Bank 2013, except Taiwan, China, which is http://www.indexmundi.com.
g. Bray and others 2013, except Hong Kong SAR, China, which is Tsoi and others 2008.

Hong Kong SAR, China, for women only (Woo, Kim, and Leung 2007), concluded that CRC screening had higher costs than for men per disability-adjusted life year saved and would not be cost-effective (CRC incidence rates in women are lower than in men).

Studies in LMICs

Two global cost-effectiveness models report estimates of cost-effectiveness of interventions for various world regions. Ginsberg and others (2010) conclude that expanding treatment in low-income countries is a higher priority than screening. Ginsberg and others (2012) come to a similar conclusion when focusing on Southeast Asia and Sub-Saharan Africa, and they conclude that screening colonoscopy is cost-effective in Sub-Saharan Africa. However, the feasibility of implementing this approach in light of resource availability and health system infrastructure limitations was not addressed.

A systematic search did not identify other studies of the cost-effectiveness of screening in LMICs. One other study was found from an unsystematic search using the Internet for the Islamic Republic of Iran (Barouni and others 2012). From the results presented, it is possible to conclude that colonoscopy every 10 years is cost-effective, but not very cost-effective, in the Islamic Republic of Iran, but that gFOBT screening is not cost-effective. There are problems with the calculation of the incremental cost-effectiveness ratios in this study, but enough information is given to permit the reader to recalculate them.

We anticipate that CRC screening would be equally cost-effective in urban areas of other upper-middle-income countries where incidence rates approach levels similar to those in HICs (30 or more per 100,000 in men, age-standardized rates). Lambert, Sauvaget, and Sankaranarayanan (2009, 255) conclude that population screening for CRC is not the highest priority in most LMICs, but that it deserves to be developed "in limited regions of large emerging countries where there is a shift to Western lifestyle and an aging population," and they point to Mumbai; Hong Kong SAR, China; and São Paulo as examples.

Treatment

No literature on the cost-effectiveness of treatment for CRC was found for LMICs. Chapter 16 summarizes the evidence of cost-effectiveness of treatment in HICs, making the assumption that treatments that are "very cost-effective" in HICs are the first candidates for consideration in MICs, while treatments that are "not cost-effective" in HICs are unlikely to be cost-effective in LMICs. This is likely to be a better guide if relative costs and "standard care"—the alternative to which a particular treatment is compared—are reasonably similar.

RECOMMENDATIONS

Country income level does not have to dictate the availability of screening, diagnosis, and treatment. Countries can help overcome resource constraints by accessing technical assistance from the IARC and international networks, or from partnerships with cancer centers or cancer agencies in other countries. Local champions are essential for moving CRC screening and treatment forward as a priority.

Table 6.2 summarizes the authors' recommendations on how screening and diagnosis for CRC might be implemented in four different resource environments: LICs, rural areas of MICs, urban areas of MICs, and HICs. These correspond approximately to the basic, limited, enhanced, and maximal resource environments for a similar exercise undertaken for breast cancer by the Global Breast Health Initiative and discussed in chapter 3. Recommendations for the treatment of CRC in these resource environments are found in online annex 6B (tables 6B.1 through 6B.5). These recommendations provide initial guidance only and need to be validated by a larger international expert group.

Low-Income Countries

In LICs, the incidence of CRC is relatively low; other diseases—including other cancers—are a higher priority for screening and treatment. Laying the foundation for cancer screening and treatment is important. This process includes investing in public health and primary health care where screening is initiated, in hospital systems, and in a cancer registry. Investments in health require medical personnel, as well as good systems for monitoring and evaluation and quality control. Smaller countries lacking specific resources, such as radiation facilities and specialized laboratories, may need to rely on other countries in the same region.

Even in LICs, surgery for colon cancer at a good district hospital is possible to save lives and improve the quality of remaining life. If colonoscopy is unavailable as a diagnostic tool, barium enema may be an option. Radiation therapy is available only in limited volumes, if at all, and laboratory services required for chemotherapy are not likely to be available. Pain management for late-stage cancers is an ethical imperative, since the ability to treat effectively is extremely limited.

Table 6.2 Proposed Strategies for Colorectal Cancer Screening and Diagnosis, by Country Resource Level

Level of resources	General	Detection and diagnosis
Basic	• Build capacity: human, physical (for example, radiation capacity), cancer registry	• Barium enema if colonoscopy not available; in emergency situations, may be diagnosed at surgery
Limited	• Establish capacity for colonoscopy (needed for diagnosis) • Engage in partnership arrangements with cancer centers to build capacity • Establish national guidelines • Build quality assurance for lab testing	• Opportunistic screening for those covered by health insurance • Diagnostic colonoscopy (or barium enema) for those with symptoms
Enhanced	• Join international screening networks • Provide support to less-well-resourced countries in region	• Establish organized screening in high-incidence cities/regions starting at age 50 years in persons at average risk: use annual or biennial sensitive gFOBT or FIT; FS (see text for discussion of interval); or colonoscopy every 10 years • Considerable infrastructure is required to support organized screening, including invitations, recalls, reminders, tracking screening test results, ensuring follow-up of those with an abnormal screening test, etc.
Maximal		• National (or jurisdiction-wide) organized screening: starting at age 50 years in persons at average risk: use annual or biennial sensitive gFOBT or FIT; FS (see text for discussion of interval); or colonoscopy every 10 years; in those at increased risk because of family history, consider colonoscopy

Note: Since no international consensus-setting exercise has occurred, this categorization represents a basis for further discussion and work and not a definitive analysis. The basic resource level is assumed to correspond to low-income countries (limited or no access to radiation and likely insufficient support for blood chemistry to undertake chemotherapy). The limited resource level corresponds to rural areas of middle-income countries, where distances to radiation and chemotherapy resources make their use in treatment difficult. In urban areas of middle-income countries (enhanced level), radiation therapy is available, as are many chemotherapy drugs no longer under patent. The maximal level corresponds to resource availability in high-income countries. See chapter 16 in this volume for more detailed discussion of resource levels. The recommendations are cumulative: any intervention that is feasible at a lower resource level is also an option at higher resource levels. Blank cells indicate that no additional options of a particular type of treatment are available at the particular resource level considered. FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test.

Middle-Income Countries

In MICs, there is an increase (more pronounced initially in urban areas) in CRC incidence and the ability to intervene. Opportunistic screening increases for those covered by health insurance. Those countries that have already begun organized screening for other cancers (including countries in Latin America and the Caribbean and upper-middle-income Asia; see chapter 12 in this volume [Sullivan, Sullivan, and Ginsburg 2015]) may decide to implement screening initially as a pilot study in selected urban regions. Other regions that are beginning organized screening for other cancers may decide to incorporate screening as well, for example, by developing programs in cities in Asia.

Priority countries are those where age-standardized CRC incidence rates in men are more than 30 per 100,000 (for example, Hungary, Serbia, and other countries in Eastern Europe), in addition to those economies with existing pilot programs, such as Argentina. Countries where CRC incidence rates in men approach 20 per 100,000 may need to begin planning (for example, countries such as Cuba, Lebanon, and Malaysia). Data are not available using GLOBOCAN for individual cities, but similar CRC incidence thresholds could be used to consider when to begin to take action on CRC screening.

For CRC screening, gFOBT is inexpensive; however, additional investments are needed to implement all the components of organized screening. MICs initiating organized CRC screening may be advised to use FIT rather than gFOBT; doing so may become more attractive if a larger demand for such tests results in a decrease in the unit costs of the kits.

MICs also have more resources for treatment and can extend this to a larger proportion of the population. As cancers are detected earlier, the goal of treatment shifts from palliation to cure. MICs can be active participants in international networks and local centers of excellence and can provide support for other countries in their region.

High-Income Countries

In HICs, cost-effectiveness considerations suggest that FIT, FS accompanied by a sensitive gFOBT or FIT, or colonoscopy are options for screening. The Republic of Korea and Singapore, which started their screening programs more recently than European countries, have opted to use FIT. Adherence to screening varies; although each test has its advocates, the best test is the one that gets done, and done well. A wider range of treatment options is feasible in these countries, which typically have higher cost-effectiveness thresholds.

CONCLUSIONS

The burden of CRC is increasing worldwide. There is an unparalleled opportunity for prevention and early detection of CRC, based on our knowledge of colorectal carcinogenesis. The implementation of effective screening tests, both stool-based (gFOBT, FIT) and endoscopic (FS, colonoscopy), coupled with advances in treatment (colonoscopic polypectomy, surgery, radiation therapy, and chemotherapy) are cost-effective approaches.

Since screening is a process, it is most effective when delivered within an organized program, requiring infrastructure and resources to ensure the benefits while minimizing the harms. CRC screening and treatment are becoming priorities in an increasing number of countries, as health resources are enhanced and changes in lifestyles and risk factors lead to a rise in incidence. Research on the cost-effectiveness of options in these countries is needed, ideally adapting available, well-constructed models to these environments. The development of regional CRC screening guidelines would be helpful; the resource-based recommendations outlined in this chapter may be useful in that process.

NOTES

World Bank Income Classifications as of July 2014 are as follows based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  a) lower-middle-income = US$1,046–US$4,125
  b) upper-middle-income (UMICs) = US$4,126–US$12,745
- High-income countries (HICs) = US$12,746 or more.

1. Maps and figures in this chapter are based on incidence and mortality estimates for ages 0–69, consistent with reporting in all DCP3 volumes. Global cancer statistics are estimates for 2012 and have been provided by the International Agency for Research on Cancer from its GLOBOCAN 2012 database. Observable population-based data were derived from *Cancer Incidence in Five Continents, 10th edition* and for trends over time from *CI5 Plus* (http://ci5.iarc.fr/CI5plus/Default.aspx). The discussion of burden, including risk factors, however, includes all ages unless otherwise noted. Interventions also apply to all age groups, except where age ranges or cutoffs are specified.

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