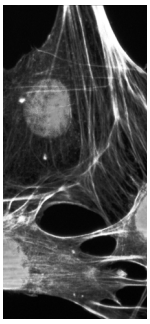

Chapter **29**

Health Service Interventions for Cancer Control in Developing Countries

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INTRODUCTION

Cancer imposes a major disease burden worldwide, with considerable geographic variations in incidence; mortality; survival; overall disease burden; causative environmental factors; and mix of prevention, detection, treatment, and palliative programs that make up a country's cancer control strategy. Unless cancer prevention and screening interventions effectively reduce the incidence of cancer, the number of new cancer cases will increase from an estimated 10 million cases in 2000 to 15 million in 2020, 9 million of which would be in developing countries. By 2050, the cancer burden could reach 24 million cases per year worldwide, with 17 million cases occurring in developing countries (Parkin, Bray, and Devesa 2001).

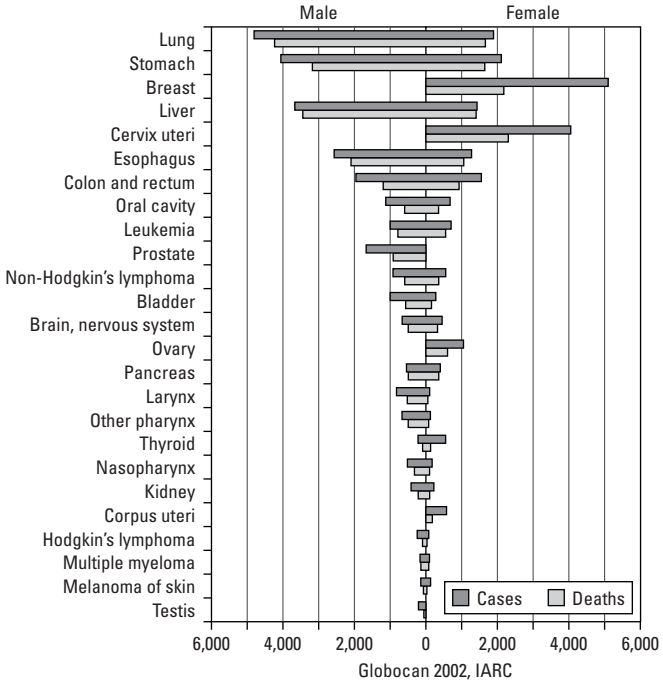
Researchers have made numerous efforts to quantify the global burden of cancer and to estimate site-specific cancer mortality and morbidity (see, for example, Ferlay and others 2004; Parkin, Bray, and Devesa 2001). A recent report from the International Agency for Research on Cancer provides estimates of cancer incidence for Africa by site and country (Parkin and others 2003). In general, however, data on cancer incidence, prevalence, and mortality are less complete and less accurate in developing countries than in developed countries, because the latter have more resources to invest in population-based cancer registries and the infrastructure to maintain such registries.

Despite the limitations of current data for developing countries, the epidemiology of cancer in developing countries clearly differs from that in developed countries in some important respects. Developed countries often have relatively high rates of lung, colorectal, breast, and prostate cancer because of the earlier onset of the tobacco epidemic, the earlier exposure to occupational carcinogens, and the Western diet and lifestyle in such countries. In contrast, up to one-fourth of cancers in developing countries are associated with chronic infections. Liver cancer is often causally associated with infection by the hepatitis B virus (HBV), cervical cancer is associated with infection by certain types of human papillomavirus (HPV), and stomach cancer is associated with *Helicobacter pylori* infection.

This chapter focuses on interventions for controlling seven cancers that impose a particularly heavy burden of disease on developing countries: cervical cancer, liver cancer, stomach cancer, esophageal cancer, lung cancer, colorectal cancer, and breast cancer. In 2000, these seven types of cancer accounted for approximately 60 percent of all newly diagnosed cancer cases and cancer deaths in developing countries (Ferlay and others 2001). Four of the seven cancers—cervical, liver, stomach, and esophageal—have elevated incidence and mortality rates in developing countries. The other three—lung, colorectal, and breast—have lower incidence and mortality rates than the other four cancers, but they nonetheless impose a heavy disease burden and are increasing because of demographic and industrial transitions. Pediatric cancers and HIV-related cancers, two topics that are of great importance and concern, are beyond the scope of this chapter.

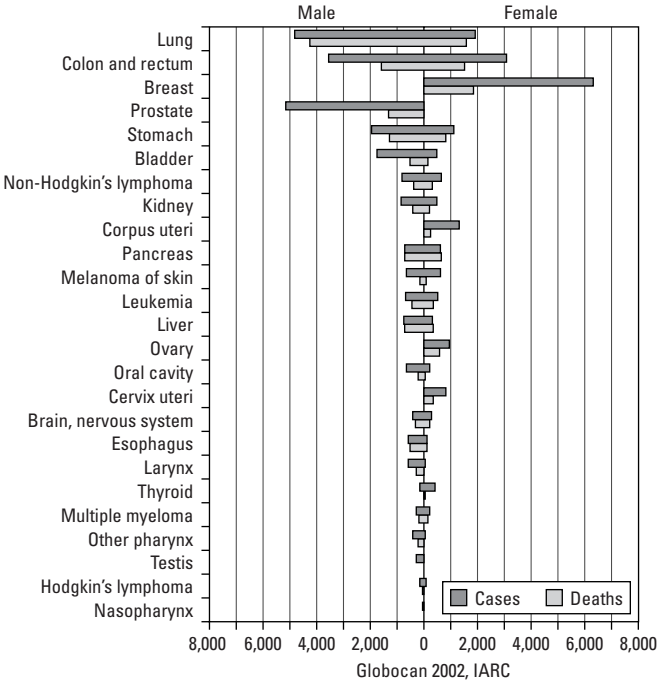
BURDEN OF CANCER IN DEVELOPING COUNTRIES

Data from Ferlay and others (2004) clearly illustrate the differing patterns of cancer incidence in developing and developed



Source: Ferlay and others 2004.

Figure 29.1 Estimated Number of Cancer Cases of All Ages, Developing Regions, 2002
(hundreds)



Source: Ferlay and others 2004.

Figure 29.2 Number of Cancer Cases of All Ages, Developed Regions, 2002
(hundreds)

countries (figures 29.1 and 29.2). In developing countries, the top five female cancers in rank order of incidence are breast, cervical, stomach, lung, and colorectal cancer; however, cervical cancer still accounts for more deaths than breast cancer in developing countries. The top five male cancers are lung, stomach, liver, esophageal, and colorectal cancer (figure 29.1). The incidence of cancers of the lung and breast is relatively high in both developed and developing countries. Colorectal cancer accounts for a smaller share of the burden in developing countries than in developed countries, but cancer of the stomach accounts for a higher share. Some cancers that are more common in developing than in developed countries, including stomach, liver, and cervical cancer, are related to the absence of a well-developed public health infrastructure for the control of cancer-causing infectious agents and contaminants, the lack of basic preventive health care and screening services for much of the population, and the poor-quality diets available to the most economically disadvantaged members of society in many developing countries. Cancer of the esophagus, also relatively common in developing countries, may reflect, in part, the consumption of traditional beverages at extremely high temperatures. Some cancers that are increasingly common in developing countries, including lung, breast, and colorectal cancer, may reflect the increasing Westernization of lifestyles, longer life expectancy, and globalization of markets for tobacco products.

For some cancers, including esophageal, liver, lung, and pancreatic cancer, survival rates vary little between developing and developed countries (Sankaranarayanan, Black, and Parkin 1998). Currently available methods of early detection and treatment have not been demonstrated to be effective for these cancers, so primary prevention remains the most practical intervention for control. For a second group of cancers, including large bowel, breast, ovarian, and cervical cancer, proven methods of early detection, diagnosis, and treatment are available that can, in principle, be delivered through district health care facilities. For these cancers, survival rates vary both between developing and developed countries as a whole and between specific countries within each of these groups. For a third group of cancers, including testicular cancer, leukemia, and lymphoma, the variability in survival between developing and developed countries is tremendous. Even though relatively effective treatments are available for these cancers, they are multimodal treatments that require a relatively high level of medical resources, a good health care infrastructure, and a level of sophisticated knowledge, which low- and middle-income developing countries may not have.

Table 29.1 shows estimated cancer deaths and the estimated disease burden in terms of disability-adjusted life years (DALYs) lost as a result of various types of cancers in developing and developed countries and by region in 2001. As the table

Table 29.1 Number of Cancer Deaths and DALYs Lost to Cancer, by World Bank Region and Country Income Level, 2001

	East Asia and the Pacific		Europe and Central Asia		Latin America and the Caribbean		Middle East and North Africa		South Asia		Sub-Saharan Africa		Low- and middle-income countries		High-income countries	
Cancer site	**Deaths**	**DALYs lost**	**Deaths**	**DALYs lost**	**Deaths**	**DALYs lost**	**Deaths**	**DALYs lost**	**Deaths**	**DALYs lost**	**Deaths**	**DALYs lost**	**Deaths**	**DALYs lost**	**Deaths**	**DALYs lost**
Trachea, bronchus, and lung cancers	387,000	5,333,000	165,000	2,323,000	55,000	728,000	20,000	283,000	129,000	1,807,000	15,000	225,000	771,000	10,701,000	456,000	5,397,000
Stomach cancer	442,000	6,134,000	101,000	1,376,000	57,000	735,000	18,000	252,000	45,000	629,000	33,000	487,000	696,000	9,616,000	146,000	1,628,000
Liver cancer	373,000	5,923,000	28,000	379,000	21,000	277,000	9,000	138,000	27,000	464,000	46,000	762,000	505,000	7,945,000	102,000	1,223,000
Esophageal cancer	232,000	3,217,000	21,000	288,000	16,000	215,000	5,000	72,000	80,000	1,116,000	24,000	343,000	380,000	5,252,000	58,000	702,000
Colorectal cancer	159,000	2,334,000	96,000	1,290,000	37,000	485,000	10,000	164,000	35,000	499,000	20,000	291,000	357,000	5,060,000	257,000	3,175,000
Breast cancer	93,000	1,730,000	63,000	1,058,000	37,000	642,000	14,000	273,000	76,000	1,246,000	34,000	574,000	317,000	5,527,000	155,000	2,509,000
Mouth and oropharyngeal cancers	66,000	1,064,000	27,000	426,000	14,000	204,000	5,000	78,000	140,000	2,020,000	19,000	284,000	271,000	4,078,000	41,000	576,000
Cervix uteri cancer	47,000	805,000	19,000	356,000	26,000	494,000	5,000	93,000	83,000	1,423,000	38,000	627,000	218,000	3,799,000	17,000	319,000
Lymphomas and multiple myeloma	42,000	753,000	23,000	375,000	24,000	383,000	12,000	232,000	82,000	1,401,000	34,000	622,000	216,000	3,770,000	115,000	1,362,000
Leukemia	76,000	1,652,000	27,000	462,000	22,000	444,000	14,000	307,000	38,000	851,000	14,000	245,000	190,000	3,965,000	73,000	919,000
Prostate cancer	16,000	164,000	25,000	283,000	37,000	340,000	6,000	64,000	21,000	210,000	40,000	416,000	145,000	1,479,000	119,000	1,212,000
Pancreatic cancer	37,000	544,000	35,000	481,000	20,000	248,000	4,000	55,000	13,000	176,000	8,000	117,000	117,000	1,621,000	110,000	1,232,000
Bladder cancer	30,000	348,000	24,000	300,000	9,000	100,000	15,000	214,000	30,000	408,000	10,000	133,000	117,000	1,504,000	59,000	670,000
Ovarian cancer	25,000	464,000	21,000	350,000	9,000	152,000	2,000	42,000	21,000	327,000	9,000	152,000	86,000	1,488,000	46,000	651,000
Corpus uteri cancer	8,000	175,000	17,000	349,000	12,000	254,000	1,000	22,000	4,000	66,000	3,000	41,000	44,000	908,000	27,000	586,000
Melanoma and other skin cancers	5,000	66,000	11,000	160,000	7,000	97,000	1,000	19,000	3,000	41,000	8,000	118,000	35,000	501,000	30,000	409,000
Other malignant neoplasms	104,000	1,640,000	123,000	1,901,000	82,000	1,263,000	26,000	440,000	26,000	1,444,000	55,000	844,000	490,000	7,538,000	257,000	3,316,000
Total (all malignant neoplasms)	2,142,000	32,346,000	826,000	12,157,000	485,000	7,061,000	167,000	2,748,000	853,000	14,128,000	410,000	6,281,000	4,955,000	74,752,000	2,068,000	25,886,000

Source: Mathers and others forthcoming.
Note: For an explanation of how DALYs are computed, see chapter 15 of this volume.

shows, the seven types of cancer that are the focus of this chapter account for seven of the first eight cancer sites ranked by number of deaths in developing countries. Considerable heterogeneity in the pattern of cancer burden across the six regions is apparent, and additional heterogeneity is apparent within these regions. Deaths from liver cancer are relatively high in East Asia and the Pacific and in Sub-Saharan Africa, probably because of the high prevalence of chronic HBV infection and the lack of adequate resources for food storage and preservation in those regions (Parkin and others 2003). The number of deaths from colorectal and breast cancer, as a proportion of all cancer deaths, is relatively high in Europe and Central Asia and in Latin America and the Caribbean, probably because those regions have increasingly adopted more Western lifestyle patterns of reproductive behavior, diet, and physical activity. The number of deaths from oral cancer is particularly high in South Asia, where the use of betel quid is common.

TYPES OF INTERVENTIONS FOR CANCER CONTROL

The World Health Organization (WHO) emphasizes that, when developing national strategies for controlling cancer, countries should consider the following four broad approaches (WHO 2002):

- *Primary prevention.* The goal of primary prevention is to reduce or eliminate exposure to cancer-causing factors, which include environmental carcinogens and lifestyle factors related to nutrition and physical activity. For the seven cancers considered here, approaches to primary prevention include immunization against, or treatment of, infectious agents that cause certain cancers; use of tobacco control programs; reduction of excessive alcohol consumption; dietary intervention; and pharmacological intervention.
- *Early detection and secondary prevention.* The main objective of early detection or secondary prevention through population-based screening programs is detection at a stage at which curative treatment is possible. Interventions for the early detection of cancer can help reduce mortality from cancer only if they are part of a wider cancer control strategy that includes effective diagnostic follow-up procedures and treatment (Anderson and others 2003). For cervical, colorectal, and breast cancer, effective methods of early detection and treatment are available, but their implementation has been uneven (Sankaranarayanan, Black, and Parkin 1998).
- *Diagnosis and treatment.* The primary modalities of cancer treatment are surgery, chemotherapy, and radiotherapy, and these modalities may be used alone or in combination. There is increasing emphasis worldwide on the development of specialized cancer centers that apply evidence-based multimodal therapies, including rehabilitation and palliative care.
- *Palliative care.* The scope of palliative care has been expanded in recent years to encompass the alleviation of symptoms and treatment during all phases of disease—from diagnosis to death—and to address matters related to the psychological and quality-of-life aspects of disease, as well as the physiological aspects. Furthermore, palliative care has been expanded to include consideration for the well-being of the patient's family members as well as for the patient (Singer and Bowman 2002).

The discussion in this chapter focuses primarily on health service interventions for controlling the seven cancers that are the subject of this chapter. Other chapters deal with broad public health interventions involving the control of occupational and environmental exposures; health education; policy interventions such as regulation, labeling, and taxation related to tobacco consumption; diet; and physical activity.

COST-EFFECTIVENESS OF CANCER CONTROL INTERVENTIONS

There is a growing literature on the cost-effectiveness of interventions within each of the four categories above. In this section, we review published studies of the cost-effectiveness of health services–based cancer control interventions, and we present new analyses of the cost-effectiveness of screening interventions for cervical and breast cancer.

Primary Prevention

This subsection reviews studies of the effectiveness and cost-effectiveness of several interventions for the primary prevention of cancer.

Immunization against—or Treatment of—Infectious Agents That Cause Certain Cancers. Infectious agents are causally associated with three of the seven cancers that are the focus of this chapter—liver cancer (HBV), cervical cancer (HPV infection), and stomach cancer (*H. pylori* infection)—so eliminating these agents through immunization or other means offers hope for preventing such cancers.

The HBV vaccine was designed to prevent liver cancer and is currently the only such vaccine in widespread use. Long-term protection against acute and chronic infection has been demonstrated with the HBV vaccine in a wide range of settings (Coursaget and others 1994; Viviani and others 1999), and recent data support a reduction in hepatocellular carcinoma (Lee, Hsieh, and Ko 2003).

Infection with specific high-risk types of HPV plays a key role in causing cervical cancer. A double-blind placebo-controlled trial of an HPV 16 vaccine reported encouraging efficacy results in young female volunteers who had been fully vaccinated (three doses of vaccine or placebo) over a 1.7-year follow-up period (Koutsky and others 2002). In a more recent study, a bivalent HPV 16/18 vaccine prevented approximately 95 percent of persistent infections with HPV 16 and 18 (Harper and others 2004).

Several modeling studies have explored the potential benefits of HPV vaccination at the population level (Goldie and others 2003; Hughes, Garnett, and Koutsky 2002; Kulasingam and Myers 2003) and have elucidated several priorities for future research, including a better understanding of the heterogeneity of vaccine response and the effects of type-specific vaccination on other HPV types.

Hughes, Garnett, and Koutsky (2002) evaluate the potential effectiveness of HPV vaccination using a dynamic transmission model and find that, when both men and women were vaccinated—assuming 90 percent coverage, 75 percent effectiveness, and 10-year immunity—type-specific HPV prevalence was reduced by 44 percent. When only women were vaccinated, the reduction was 30 percent. The authors show that, if the vaccine targeted only certain types of high-risk HPV, cervical cancer incidence was not reduced proportionally because other high-risk types of HPV progressed to invasive cancer.

Goldie and others (2003) assess the impact of a type-specific HPV 16/18 vaccine calibrated to population-based data for Costa Rica. They find that a vaccine that prevented 98 percent of persistent HPV 16/18 was associated with an approximate equivalent reduction in HPV 16/18–associated cancer and a 51 percent reduction in total cervical cancer. The effect on total cancer was attenuated because of the competing risks associated with oncogenic types of HPV other than HPV 16/18.

Three studies have evaluated the potential cost-effectiveness of HPV vaccination in countries with cervical cancer screening programs (Goldie, Kohli, and others 2004; Kulasingam and Myers 2003; Sanders and Taira 2003). In general, these studies indicate that a program of HPV vaccination that permits a later age of screening initiation and a less frequent screening interval is likely to be a cost-effective use of health care resources in developed countries.

In Fujian province, China, a region of high mortality attributable to stomach cancer, a recently completed randomized controlled trial of *H. pylori* eradication with antibiotics provides some evidence that this approach may be effective in preventing stomach cancer in the subgroup of *H. pylori* carriers without precancerous lesions at the time of treatment (Wong and others 2004). A recent randomized trial of *H. pylori* eradication in Chiapas, Mexico, which used preneoplastic conditions as surrogate markers for the development of gastric cancer, found some evidence for the effectiveness of this treatment (Ley and others 2004).

Several studies, most of them in developed countries, have assessed the potential cost-effectiveness of screening individuals for infection with *H. pylori* and then eradicating *H. pylori* with antibiotic therapy as a means of preventing the later occurrence of stomach cancer. Roderick and others (2003) examine the cost-effectiveness of an *H. pylori* screening program conducted in the United Kingdom. Discounting costs and benefits at 6 percent, they find that the cost-effectiveness ratio for screening for *H. pylori,* initiated at age 40, is approximately US$28,000 per year of life saved (YLS). Optimal cost-effectiveness was not achieved until the *H. pylori* screening program had run for at least 40 years. Harris and others (1999) estimate the cost-effectiveness ratio associated with one-time screening for *H. pylori* at age 50 to be approximately US$50,000 per YLS (in 1995 dollars, 3 percent discount rate) when treatment for *H. pylori* infection results in a 15 percent reduction in stomach cancer risk. Assuming a 30 percent reduction, the figure was US$25,000 per YLS for the United States, but only a few hundred dollars per YLS in Colombia, which has a much higher rate of stomach cancer and lower health care costs.

Tobacco and Alcohol Control Programs. Tobacco consumption is the most important cause of lung and other cancers of the respiratory system, as well as of esophageal cancer, and may be a contributing factor for several other cancers. The most effective national tobacco control programs combine health promotion, education, and health service interventions with policies. Policy instruments include regulating tobacco advertising and promotion; enacting smoking bans in workplaces, restaurants, and public buildings and on public transportation; and increasing excise taxes on tobacco products (Fiore, Hatsukami, and Baker 2002; WHO 2002). Decreased rates of smoking uptake by children and adolescents would result in the greatest potential gain in life years. The WHO Framework Convention on Tobacco Control (WHO 2003b) summarizes tobacco control policies and programs related to regulation, taxation, and education. Da Costa e Silva (2003) shows prioritized treatment approaches for tobacco cessation, based on countries' levels of resources.

Excessive alcohol use accounts for 20 to 30 percent of liver and esophageal cancer (WHO 2001b). Interventions to reduce excessive consumption of alcohol have many principles in common with tobacco control, including the effectiveness of regulatory and taxation measures along with health promotion and addiction treatment programs.

Dietary and Related Interventions. The dietary ingestion of substances produced by the mold *Aspergillus flavus,* specifically aflatoxin B1, is causally associated with hepatocellular carcinoma. Exposure to aflatoxins may be synergistic with HBV

infection in the development of this cancer. Effective means are available for preventing the contamination of grains and other types of food with aflatoxin during the growth, harvest, storage, and processing of such products (Kensler and others 2003; Turner and others 2002). Furthermore, chlorophyllin supplements have been found to reduce the carcinogenic properties of aflatoxin. That finding provides additional evidence for current dietary guidelines that meals should contain foods rich in chlorophylls—for example, spinach and other green, leafy vegetables (Kensler and others 2003).

Among those infected with *H. pylori,* diet is thought to play a critical role in the progression of superficial gastritis to chronic atrophic gastritis. Prolonged consumption of foods rich in salted, pickled, and smoked products increases the risk of stomach cancer, and increased consumption of fresh fruit and vegetables likely decreases the risk. Obesity is also a well-established risk factor for several cancers (Vainio and Bianchini 2002b). For that reason, WHO recommends that governments seeking to ensure compliance with nutritional objectives conduct appropriate school and public education campaigns on diet and work with the food and agriculture sectors (WHO 2002).

Pharmacological Interventions. *Chemoprevention* is defined as the reduction of the risk of cancer development through the use of micronutrients or pharmaceuticals. Clinical trials among high-risk individuals to establish the efficacy of chemoprevention via micronutrients (for instance, carotenoids and retinoids) and dietary fiber have been mainly negative (Alberts and others 2000; ATBC 1994; Omenn and others 1996; Schatzkin and others 2000). However, several ongoing clinical studies are examining the potential cancer preventive effects of calcium, vitamin D, folic acid, selenium, and vitamin E (Christensen 2004).

Both case-control and cohort studies show a reduced risk for colorectal cancer after prolonged use of aspirin (Vainio and Morgan 1999). Additional evidence indicates that aspirin has a preventive effect on several other types of cancer, including hormone receptor–positive breast cancer (Terry and others 2004), but questions remain about the balance between the clinical benefits and adverse side effects of long-term aspirin therapy, including gastrointestinal bleeding and hemorrhagic stroke (Imperiale 2003).

Some evidence suggests that the antiestrogen drug tamoxifen may reduce the risk of breast cancer (Gail and others 1999), but there is also conflicting evidence (Powles and others 1998; Veronesi and others 1998). The potential for primary prevention using other selective estrogen receptor modulators is a topic of current clinical research (Lippman, Lee, and Sabichi 1998). Preliminary analyses indicate that the use of tamoxifen to prevent breast cancer could be cost-effective in the United States (T. Smith and Hillner 2000).

Early Detection and Secondary Prevention

This subsection looks at studies of the effectiveness and cost-effectiveness of several interventions for the early detection and secondary prevention of cancer.

Screening for Liver Cancer. Screening methods for early detection of liver cancer include serum assays for alpha-fetoprotein and, potentially, ultrasound. A recently completed randomized controlled trial of liver cancer screening in China evaluated the use of two or six alpha-fetoprotein assays over a period of four years among men age 30 to 69 with chronic HBV (Chen and others 2003). Screening resulted in earlier diagnosis of liver cancer, but because treatment for established liver cancer is largely ineffective, screening did not reduce overall mortality.

Randomized trials that include ultrasound screening for liver cancer and that incorporate recent advances in antiviral preventive treatment have yet to be conducted. Sarasin, Giostra, and Hadengue's (1996) model-based cost-effectiveness analysis explores whether biannual screening of patients with Child-Pugh class A cirrhosis, under a set of assumptions systematically favorable to screening, would be cost-effective. The authors conclude that, even under best-case conditions, screening for liver cancer is not likely to be cost-effective.

Screening for Stomach Cancer. Mass screening programs for the early detection of invasive stomach cancer using radiological or endoscopic techniques have been widely implemented in Japan, where incidence rates of stomach cancer are high.

Babazono and Hillman (1995) compare the cost-effectiveness of three methods for the early detection of stomach cancer in the context of mass screening programs in Japan: indirect radiology (barium meal plus photofluoroscopy), direct radiology, and endoscopy. When screening for stomach cancer was started late in life, indirect radiology was the most cost-effective screening method. This analysis supports an increase in the recommended age for initiating screening for stomach cancer from age 40 to 50.

Screening for Lung Cancer. Investigators have carried out several cost-effectiveness analyses of the screening of high-risk individuals, such as current and former smokers, for lung cancer using helical computed tomography (Chirikos and others 2002; Mahadevia and others 2003; Marshall and others 2001). The results of these studies vary widely from quite favorable (US$19,000 per YLS) to extremely unfavorable (more than US$100,000 per YLS). The main reason for the wide variation in these studies is different assumptions about the clinical nature of early lung lesions detected by helical computed tomography—specifically, whether a large proportion of these

Table 29.2 Estimates of the Cost-Effectiveness of Colorectal Cancer Screening Interventions, United States
(cost-effectiveness ratios expressed as 2000 US$/YLS)

Colorectal screening test	Wagner and others 1996	Frazier and others 2000	Khandker and others 2000	Sonnenberg, Delco, and Inadomi 2000	Vijan and others 2001
Annual fecal occult blood test	11,725	17,805	13,656	10,463	5,691
Flexible sigmoidoscopy every 5 years	12,477	15,630	12,804	39,359	19,058
Flexible sigmoidoscopy every 5 years and annual fecal occult blood test	13,792	22,518	18,693	n.a.	17,942
Double-contrast barium enema every 5 years	11,168	21,712	25,624	n.a.	n.a.
Colonoscopy every 10 years	10,933	21,889	22,012	11,840	9,038

Source: Pignone and others 2002.
n.a. = not applicable.
Note: All costs and life years are discounted at 3 percent, except in the study by Wagner and others (1996), who use a discount rate of 5 percent.

small lung nodules represents "pseudo-disease" that will never progress to clinical lung cancer (Marcus and others 2000). The National Lung Cancer Screening Trial, currently under way (van Meerbeeck and Tournoy 2004), hopes to answer this question. Until results from the trial are available, no definitive statement can be made about the effectiveness or cost-effectiveness of lung cancer screening.

Screening for Colorectal Cancer. Screening methods for early detection of colorectal cancer include fecal occult blood testing, sigmoidoscopy, barium enema, and colonoscopy. Several studies of the cost-effectiveness of colorectal cancer screening in developed countries have been published (Pignone and others 2002). Table 29.2 presents estimates of the cost-effectiveness of colorectal cancer screening in the United States. Cost-effectiveness ratios for various modalities of colorectal cancer screening range from almost US$6,000 to about US$40,000 per YLS. Using models closely linked to European trials of biennial fecal occult blood testing to screen for colorectal cancer, Whynes and Nottingham Faecal Occult Blood Screening Trial (2004) report favorable cost-effectiveness ratios ranging from US$2,500 to US$4,000 per YLS. Studies of the cost-effectiveness of colorectal cancer screening in developed countries consistently conclude that such screening is cost-effective, but they do not totally agree on the relative rankings of different colorectal screening strategies (Pignone and others 2002).

Screening for Cervical Cancer. Cytology-based screening using the Papanicolaou smear has been the main screening method used for the secondary prevention of cervical cancer worldwide. In many low-income countries, however, cytology screening has proved difficult to sustain because of its reliance on highly trained cytotechnologists; good-quality laboratories; and infrastructure to support up to three visits for screening, evaluation of cytologic abnormalities with colposcopy, and treatment (Sankaranarayanan, Budukh, and Rajkumar 2001). Two alternative screening approaches replace the Pap smear with simple visual screening methods, such as visual inspection after application of an acetic acid solution (VIA), or with HPV DNA testing (Denny and others 2000; Sankaranarayanan and others 1999; Schiffman and others 2000; Wright 2003; Wright and others 2000; Zimbabwe Project 1999). These newer options also eliminate colposcopy, potentially allowing screening and treatment to be performed during the same visit. In middle-income countries where cytology screening is available but cervical cancer mortality has not been reduced, key questions center around improving the quality of cytology-based programs; such improvement includes having adequate colposcopy and biopsy facilities and accessible treatment (Lazcano-Ponce and others 1999); making use of HPV DNA testing technology in a cost-effective manner; and targeting the appropriate age group for cervical cancer screening more accurately. The vast majority of published cost-effectiveness analyses of population-based cervical cancer screening performed during 1980–2003 focused on high-income countries. (A list of the 39 studies reviewed is available from the authors.) The detailed results of each study are somewhat difficult to compare. The types of costs included in each study varied substantially (patient time costs and programmatic costs often were omitted), studies frequently did not discount costs and benefits or did not note the discount rate used, and sensitivity analyses were not conducted consistently on all relevant variables. Despite those limitations, several themes emerge. The incremental cost-effectiveness of screening in the general population becomes increasingly less favorable as programs are intensified by shortening the screening interval. For example, Mandelblatt and others (2002) reported that for conventional cytology and HPV testing, compared with cytology alone, the incremental cost was more than US$300,000 when conducted annually compared to US$15,400 per YLS when conducted every 10 years. Maxwell and others (2002) reported that liquid-based cytology and HPV testing for equivocal results cost US$231,300 per YLS if conducted annually incremental to 14,300 per YLS if conducted every three years. Kim Wright, and

Goldie (2002) reported similar results for this same strategy (US$20,300 per YLS conducted every five years, US$59,600 per YLS every three years, and US$174,200 every two years). The analyses, which included strategies that employed both frequent screening and screening tests with higher sensitivity, often found the cost-effectiveness of frequent screening to be even less attractive. For example, Goldie, Kim, and Wright (2004) reported annual screening with combined cytology and HPV DNA testing in women over age 30 exceeded US$1 million per YLS compared to every two years. Although many analyses find that extending the age range to the very young, the very old, or both can be less cost-effective, for certain women in high-risk groups, including older, uninsured women who have never been screened, screening for cervical cancer at older ages can be cost-effective.

The analyses conducted in low-income countries focused on assessing the cost-effectiveness of an expanded set of strategies that included alternatives to conventional cytology. In addition, these analyses—unlike those in developed regions—often raised issues of feasibility, affordability, cultural context, accessibility, and equity.

In one of the earliest stochastic modeling evaluations of cervical cancer screening programs in developing regions, Sherlaw-Johnson, Gallivan, and Jenkins (1997) explored the effectiveness of cytology and HPV testing in the context of infrequent screening. They reported that the most efficient use of resources would be to concentrate cervical cancer screening efforts on women age 30 to 59 at least once per lifetime, because such blanket screening would reduce the incidence of invasive cervical cancer by up to 30 percent.

In an analysis focused on cervical cancer control in Vietnam, Suba and others (2001) reported that, because of the low direct medical costs associated with Vietnam's cervical cytology program, such a program appeared to be attractive for that country. They found that total costs to establish a nationwide Pap screening program based on five-year intervals averaged less than US$148,000 annually during the 10 years the authors assumed would be necessary to develop the program. Assuming 70 percent participation in the program, the authors found the cost-effectiveness ratio for cervical cytology screening, compared with no screening, to be US$725 per discounted YLS.

Goldie and others (2001) assessed the cost-effectiveness of several cervical cancer screening strategies in previously unscreened 30-year-old South African women. Screening tests included VIA, cytology, and HPV DNA testing. Strategies differed by the number of clinic visits required, frequency of screening and individual's age at the time of screening, and response to a positive test result. The authors found that when all strategies were considered to be equally available and were compared incrementally, HPV DNA testing was always more effective and less costly than cytology and generally more effective but more costly than VIA. They found that, in comparison with no screening, a single lifetime VIA screen at age 35, coupled with immediate treatment of women with positive results, resulted in a cost saving of US$39 per YLS as compared with a two-visit HPV, although programmatic costs were not considered. Using sensitivity analysis, the authors find the choice between using HPV DNA testing or VIA depended on the relative costs and sensitivity of the two tests and on the percentage of women lost to follow-up between the first and second visit.

Mandelblatt, Lawrence, Gaffikin, and others (2002) used a simulation model to compare seven cervical cancer screening techniques in Thailand. Comparing each strategy to the next less expensive alternative, the authors found that VIA performed at five-year intervals in women age 35 to 55, followed by immediate treatment of abnormalities, was the least expensive option and saved the greatest number of lives.

The Alliance for Cervical Cancer Prevention used primary data from studies conducted in India, Kenya, Peru, South Africa, and Thailand to develop a series of standardized, country-specific cost-effectiveness analyses. The costs and benefits associated with alternative strategies to reduce cervical cancer mortality were estimated for these five countries with different epidemiological profiles by integrating country-specific data from each site and using a standardized set of assumptions agreed on by an expert panel with experience in each country (Goldie, Gaffikin, and others 2004). In all five countries, lifetime cancer risk was reduced by approximately 25 to 35 percent with a single lifetime screen using either one-visit VIA or two-visit HPV DNA testing targeted at women age 35 to 40. Risk was reduced by more than 50 percent if screening was performed two or three times per lifetime. Although the cost of screening differed considerably between the countries, strategies were identified that, when performed two or three times per lifetime, would be considered extremely cost-effective depending on the individual country's per capita gross domestic product.

We conducted an exploratory analysis to evaluate the potential cost-effectiveness of cervical cancer screening strategies in Brazil, Madagascar, and Zimbabwe using computer-based simulation models calibrated to age-specific cervical cancer incidence and mortality in each country, along with published data. We evaluated once-in-a-lifetime screening between age 35 and 40 with (a) one-visit VIA, with screening and treatment conducted during the same visit; (b) two-visit HPV DNA screening, with HPV DNA testing during the first visit followed by treatment of screen-positive women during the second visit; and (c) three-visit cervical cytology screening, with a cytology sample obtained during the first visit, colposcopy for screen-positive women conducted during the second visit, and treatment provided during the third visit. We assumed that for the one- and two-visit strategies, women who screened positive and were eligible for cryotherapy were treated immediately, but

Table 29.3 Economic Outcomes of Once-in-a-Lifetime Cervical Cancer Screening Programs, Brazil, Madagascar, and Zimbabwe

Category	No screening	One-visit VIA	Two-visit HPV DNA testing	Three-visit cytology
Brazil				
Lifetime cost (international $)	68.41	75.08	77.43	121.12
Cost-effectiveness ratio (international $/YLS)*	n.a.	113	155	1430
Cost-effectiveness ratio (US$/YLS)	n.a.	54	118	572
Life expectancy gain per 1 million screened	n.a.	59,100	58,200	36,900
Number of deaths averted per 1 million screened	n.a.	10,399	10,235	6,411
Number of DALYs averted per 1 million screened	n.a.	56,646	55,751	35,174
Madagascar				
Lifetime cost (international $)	25.22	32.98	40.41	51.91
Cost-effectiveness ratio (international $/YLS)*	n.a.	167	332	921
Cost-effectiveness ratio (US$/YLS)	n.a.	52	162	368
Life expectancy gain per 1 million women screened	n.a.	46,500	45,800	29,000
Number of deaths averted per 1 million women screened	n.a.	8,815	8,676	5,438
Number of DALYs averted per 1 million women screened	n.a.	42,424	41,754	26,352
Zimbabwe				
Lifetime cost (international $)	31.10	39.69	44.81	61.93
Cost-effectiveness ratio (international $/YLS)*	n.a.	140	227	803
Cost-effectiveness ratio (US$/YLS)	n.a.	42	114	321
Life expectancy gain per 1 million screened	n.a.	61,300	60,400	38,400
Number of deaths averted per 1 million screened	n.a.	10,412	10,248	6,419
Number of DALYs averted per 1 million screened	n.a.	53,770	52,921	33,472

Source: Authors' calculations.
n.a. = not applicable.
*Converted from national currency, using purchasing power parity (PPP) exchange notes.

those ineligible for cryotherapy were referred for colposcopy and diagnostic workup.

We estimated direct medical costs using data from the literature and unit costs provided by the volume editors and WHO. All costs for the analysis are presented in 2000 dollars. We estimated patients' time costs and direct nonmedical costs using our own previous work and wage estimates based on World Bank data on per capita gross national income (WHO n.d.) and wage estimate regressions developed by the U.S. Department of Commerce. Table 29.3 presents the results of our analysis.

Lifetime costs per individual screened are given in international dollars. Cost-effectiveness ratios are provided in U.S. dollars as well as international dollars to facilitate comparison to other studies. The available data show that cervical cancer screening conducted once, twice, or three times in a lifetime can have a significant effect on the lifetime risk of cervical cancer compared with no screening. For countries with limited resources, screening efforts should target women age 35 or older; strategies should focus on screening all women at least once in their lifetime before increasing the frequency of screening; and countries should consider alternative approaches to the conventional three-visit cervical cytology screening techniques—for example, single-visit VIA, followed by immediate treatment, or HPV DNA testing or cervical cytology followed by treatment at a second visit. Note that all screening tests may not be equally available in low-resource settings and that certain screening tests may be selected because of cultural preferences or for programmatic reasons. Implementing cervical cancer screening programs on the basis of VIA, HPV DNA testing, or cytology requires different types of resources, and the relative availability of these resources in different settings will affect the choice of strategy.

Screening for Breast Cancer. Methods for early detection of breast cancer include screening by mammography, clinical breast examination (CBE), and breast self-examination. Screening by mammography, CBE, or both may decrease breast cancer mortality, but uncertainty about the magnitude of the benefit remains because the quality of the evidence varies and results are inconsistent (Humphrey and others 2002). Recent controlled studies of organized breast self-examination programs indicate that this approach is not effective (Semiglazov and others 1999; Thomas and others 2002).

A randomized controlled trial of CBE screening for breast cancer began in Manila in 1995, but the intervention was

discontinued after the first round because compliance with referral among women who were found to have a breast lump was extremely low (21 percent) and attempts to improve compliance failed. Analysis of the incidence of cancer cases in 1999 shows that the screening intervention succeeded in detecting more localized breast tumors, but the low compliance with referral and low yield of early cancers meant that the early detection program could not succeed in preventing deaths from breast cancer (International Agency for Research on Cancer n.d.).

Numerous cost-effectiveness studies of breast cancer screening programs have been conducted in developed countries (Vainio and Bianchini 2002a). Most cost-effectiveness studies of mammography screening in Europe yield cost-effectiveness ratios in the range of US$3,000 to US$10,000 per YLS, whereas those in the United States yield far less favorable cost-effectiveness ratios, ranging from US$20,000 to US$100,000 per YLS (table 29.4).

To investigate the potential cost-effectiveness of CBE and mammography for India, we used a microsimulation model of breast cancer screening (van Oortmarssen and others 1990). The model simulates individual life histories of disease states, and consequences of screening are calculated by comparing the histories with and without screening intervention for each individual. For our purposes, we assumed a population of 1 million Indian women with the age distribution of the country in 2000 (United Nations Population Division 2003). We assumed that the screening program would last for 25 years and would have an attendance rate of 100 percent. We expressed the effects of screening as the reduction in the number of deaths caused by breast cancer and the number of life years gained because of the screening program. Costs and effects were discounted at a rate of 3 percent.

Table 29.4 Estimates of the Cost-Effectiveness of Breast Cancer Screening Every Two Years for Women in Selected Developed Countries

Country	Age of women being screened (years)	Cost-effectiveness ratio (US$/YLS)[a]
Australia (de Koning 2000)	50–69	7,680
France (de Koning 2000)	50–69	4,580
Germany (de Koning 2000)	50–69	8,880
Netherlands (de Koning 2000)	50–69	3,140
Norway (Norum 1999)	50–69	14,790
Spain (de Koning 2000)	50–69	6,590
Spain, Catalonia (de Koning 2000)	50–69	4,400
Spain, Navarra (de Koning 2000)	45–65	2,450
United Kingdom (de Koning 2000)	50–69	2,680
United Kingdom (northwest) (de Koning 2000)	50–64	3,650
United States (M. Brown and Fintor 1993)	50–69	34,600
United States (Simpson and Snyder 1991)	50–64	20,611

Source: M. Brown and Fintor 1993; de Koning 2000; Norum 1999; Simpson and Snyder 1991.
Note: The discount rate used was 5 percent.
a. Converted from euros to U.S. dollars, using the exchange rate €1 = US$0.925.

We estimated the model's parameters using data from Dutch screening projects (Collette and others 1992; Vervoort and others 2004). We used trial results to estimate the effectiveness of mammography in reducing breast cancer mortality (de Koning and others 1995). We based sensitivity estimates of CBE on data from Rijnsburger and others (2004) and based alternative (lower) estimates on data from Bobo, Lee, and Thames (2000) and Rijnsburger and others (forthcoming). We calibrated the model so that it would correctly predict the age-specific incidence and mortality of breast cancer in India (Ferlay and others 2001) and its stage distribution at clinical diagnosis (Sankaranarayanan, Black, and Parkin 1998). Details of these methods are available elsewhere (Lamberts and others 2004).

We calculated total costs by comparing the differential costs of breast cancer screening, diagnosis, initial therapy, adjuvant therapy, follow-up, and advanced disease in the case of screening versus no screening. We calculated component costs by multiplying the estimated resource use by the estimated costs per unit for each health care input. Reliable cost data for India were limited, so we extrapolated estimates from Dutch unit costs (Mulligan and others 2003). For the analysis discussed above, we calculated costs based on a market-basket approach.

The overall incidence of breast cancer is lower in India than in Western countries. The relationship between the incidence of breast cancer and age also differs: in Western countries, the incidence of breast cancer increases with age, whereas in India, it decreases with age, beginning at age 50. Investigators have generally attributed this finding to a cohort effect: breast cancer is more common among younger cohorts than older cohorts. The stage at which breast cancer is diagnosed is much less favorable in India than in Western countries.

Table 29.5 presents the results of our exploratory cost-effectiveness analysis of various breast cancer screening programs involving CBE or mammography for a population of 1 million women in India. As the table shows, biennial CBE from age 40 to 60 costs US$2.6 million, averts 358 breast cancer deaths, prevents the loss of 4,896 life years, and has a cost-effectiveness ratio of US$522 per YLS in comparison with no screening. Biennial CBE from age 50 to 70 is less favorable in terms of cost-effectiveness: US$582 per YLS.

The cost-effectiveness ratios for biennial mammography screening are not as favorable as those for biennial CBE screening. Annual CBE screening results in almost the same number of life years saved as biennial mammography screening at 36 percent of the cost.

Table 29.5 Cost-Effectiveness Analysis of Various Breast Cancer Screening Programs Involving Either CBE or Mammography for a Population of 1 Million Women, Compared with No Screening, India

Category	Base model: biennial CBE, ages 40–60	Annual CBE, ages 40–60	Biennial CBE, ages 50–70	CBE once every 5 years, ages 40–60	Biennial mammography, ages 40–60	Biennial mammography, ages 50–70	One lifetime mammogram, age 50
Number of screening tests performed	2,319,839	4,426,854	1,620,568	1,056,544	2,318,641	1,619,051	212,008
Number of cancers detected by screening	1,689	2,330	1,683	938	2,561	2,649	465
Number of deaths averted	358	528	313	184	599	557	105
Number of life years saved	4,896	7,242	3,464	2,462	7,955	6,180	1,422
Percentage reduction in mortality	7.8	11.4	6.8	4.0	13.0	12.1	2.3
Number of screening tests per death averted	6,473	8,385	5,170	5,730	3,868	2,909	2,028
Number of screening tests per life year saved	474	611	468	429	291	262	149
Number of screening tests per cancer detected	1,373	1,900	963	1,127	906	611	456
Differential costs (2001 US$)	2,553,425	5,230,303	2,017,186	1,108,883	14,681,387	10,559,356	1,282,024
Cost per death prevented (2001 US$)	7,125	9,907	6,435	6,014	24,493	18,970	12,262
Cost per life year saved (2001 US$)	522	722	582	450	1,846	1,709	902

Source: Authors' calculations.
Note: The discount rate used was 3 percent.

Table 29.6 shows the results of our sensitivity analysis for the exploratory cost-effectiveness analysis of breast cancer screening in India. Cost-effectiveness ratios are lower when the incidence of cancer is higher, as in Bombay. Cost-effectiveness ratios are 32 and 16 percent higher, respectively, with a lower sensitivity of CBE and when the averted costs of palliative treatment are not included. Using alternative approaches to estimate screening program costs has a major effect, resulting in cost-effectiveness estimates 6 to 11 times higher than the base case analysis. This result underlines the need for economic studies that can obtain reliable data from primary sources on the true resource costs of cancer control interventions in developing countries. With data from such studies, researchers would not have to continue to rely on extrapolating cost estimates from data in developed countries.

These results depend critically on assumptions about the efficacy of CBE, for which the evidence is limited, highlighting the need for controlled studies of CBE in developing countries. Our estimates indicate that the cost-effectiveness of screening mammography in India compares favorably, in absolute terms, with breast cancer screening in developed countries. Nevertheless, screening mammography for breast cancer is likely to be less cost-effective in a country such as India than is screening for cervical cancer.

Cancer Treatment and Palliative Care

Barnum and Greenberg (1993) used an indirect approach to estimate the cost-effectiveness of initial cancer treatment in developing countries. They assumed that they could estimate the effectiveness of initial cancer treatment by comparing cancer survival in the United States for the period 1975–80 with the period 1940–45. The logic of such a comparison is that major advances in cancer diagnosis, surgery, radiation, and chemotherapy occurred during the intervening period, and thus survival in the 1940–45 period could be equated to outcomes expected to result from no treatment or ineffective treatment. Barnum and Greenberg's results indicated a cost-effectiveness ratio of the following:

- US$1,300 to US$6,200 per YLS for initial treatment of the more treatable cancers, that is, cervical, breast, oral cavity, and colorectal cancer
- US$53,000 to US$163,000 per YLS for initial treatment of the less treatable cancers, that is, liver, lung, stomach, and esophageal cancer.

The following subsections review cost-effectiveness studies performed on selected adjuvant or palliative cancer treatments that have been studied extensively in controlled clinical trials.

Table 29.6 Sensitivity Analysis for Changes in Breast Cancer Incidence and Attendance Rate, CBE Sensitivity, No Palliative Treatment, and Alternative Cost Estimates for a Population of 1 Million Women, Compared with No Screening, India

Category	Base model: biennial CBE, ages 40–60	Incidence of breast cancer, Bombay	Attendance rate, 70%	CBE sensitivity[a]	No palliative treatment	Alternative cost estimation	
						Method 1[b]	Method 2[c]
Effectiveness							
Number of screening tests performed	2,319,839	2,319,991	1,624,401	2,320,051	2,319,839	2,319,839	2,319,839
Number of cancers detected by screening	1,689	1,921	1,229	1,370	1,689	1,689	1,689
Number of deaths averted	358	405	255	286	358	358	358
Number of life years saved	4,896	5,400	3,483	3,893	4,896	4,896	4,896
Percentage reduction in mortality	7.8	6.9	5.5	6.2	7.8	7.8	7.8
Number of screening tests per death averted	6,473	5,727	6,358	8,119	6,473	6,473	6,473
Number of screening tests per life year saved	474	430	466	596	474	474	474
Number of screening tests per cancer detected	1,373	1,208	1,322	1,693	1,373	1,373	1,373
Cost-effectiveness							
Differential costs (2001 US$)	2,553,425	2,505,274	1,798,662	2,684,628	2,983,754	28,814,056	16,532,879
Cost per death prevented (2001 US$)	7,125	6,184	7,040	9,395	8,325	80,396	46,130
Cost per life year saved (2001 US$)	522	464	516	690	609	5,885	3,377

Source: Authors' calculations.
Note: The discount rate used was 3 percent.
a. From Rijnsburger and others forthcoming.
b. Costs using 2001 prices in the Netherlands.
c. Costs using 2001 prices in the Netherlands multiplied by the ratio of gross domestic product shares spent on health care in India and the Netherlands, respectively.

Table 29.7 Cost-Effectiveness of Selected Breast Cancer Treatments for a Hypothetical Cohort of 45-Year-Old Premenopausal Women with Early-Stage Breast Cancer, United States
(cost in 2000 US$/quality-adjusted life year)

Treatment	Node-negative, estrogen receptor–positive	Node-negative, estrogen receptor–negative	Node-positive, estrogen receptor–positive	Node-positive, estrogen receptor–negative
Tamoxifen	17,400	326,800	6,600	88,300
Chemotherapy	17,400	7,600	14,000	7,500
Tamoxifen and chemotherapy	50,400	131,600	22,600	123,200

Source: T. Smith and Hillner 1993.

Breast Cancer Treatment Interventions. The following paragraphs review studies of the cost-effectiveness of adjuvant systemic therapy for early-stage breast cancer and of radiation therapy following mastectomy and chemotherapy to treat node-positive breast cancer in premenopausal women.

T. Smith and Hillner (2000), relying on results from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG 1998), modeled the natural history of breast cancer in premenopausal 45-year-old women in the United States who were diagnosed with early-stage breast cancer and treated with tamoxifen, chemotherapy, or both. Table 29.7 summarizes the cost-effectiveness of various breast cancer treatments. Smith and Hillner's cost-effectiveness estimates for single-modality systemic adjuvant therapy for breast cancer are about the same order of magnitude as Barnum and Greenberg's (1993) estimates of cost-effectiveness for initial therapy of breast cancer (about US$7,300 per YLS in 2000 dollars). Other studies (Malin and others 2002; Norum 2000) have yielded cost-effectiveness estimates for chemotherapy and hormonal therapy two to three times more favorable than Smith and Hillner's estimates. The more favorable estimates are probably the result of the investigators' use of a discount rate of 3 percent instead

of 5 percent and their assumption that the benefits of treatment continue over a longer period of time.

Two U.S. studies (Lee and others 2002; Marks and others 1999) have estimated the cost-effectiveness ratio for radiation therapy following mastectomy and chemotherapy for node-positive breast cancer in premenopausal women to be in the range of US$22,600 to US$43,000 per quality-adjusted life year (adjusted to 2000 U.S. dollars, with a discount rate of 3 percent). Results were sensitive to treatment costs, survival benefit, and patient time costs.

The clinical trials of postmastectomy radiation on which the two U.S. studies are based compared radiation following surgery plus chemotherapy with surgery plus chemotherapy alone. Love and others (2003), however, offer observational evidence that radiation treatment may also extend survival for Chinese and Vietnamese women when administered to patients with one to three positive nodes following mastectomy alone or mastectomy combined with oophorectomy and tamoxifen. If these benefits were confirmed, postmastectomy radiation might be cost-effective in developing countries, where the cost of radiation treatment is lower than in most developed countries.

Colorectal Cancer Treatment Interventions. As concerns colorectal cancer, investigators have carried out cost-effectiveness studies on surgical techniques, adjuvant treatment, follow-up monitoring for recurrence, and treatment of advanced disease (van den Hout and others 2002). Brown, Nayfield, and Shibley (1994) estimate that the cost-effectiveness of adjuvant chemotherapy for stage three colon cancer ranges from US$3,000 to US$7,000 per YLS (adjusted to 2000 U.S. dollars, with a discount rate of 6 percent). R. Smith and others' (1993) study conducted in the Australian health care setting obtains similar results in terms of cost per YLS but yields substantially higher costs per quality-adjusted life year.

Dahlberg and others' (2002) cost-effectiveness study, which relies on cost and clinical outcome data from the Swedish Rectal Cancer Trial (1997), demonstrates that rectal cancer patients receiving preoperative radiation therapy had improved cancer-specific and overall survival rates, as well as reduced local rectal cancer recurrence rates. They estimate the overall cost-effectiveness of preoperative radiation therapy for rectal cancer patients to be US$3,654 per YLS (in 2001 U.S. dollars, using a discount rate of 3 percent). In a sensitivity analysis, which varied the rates of local rectal cancer recurrence and the survival advantage with and without radiation treatment, cost-effectiveness ratios for preoperative radiation therapy for patients with rectal cancer ranged from US$908 to US$15,228 per YLS.

Cervical Cancer Treatment Interventions. Five recent phase 3 trials indicate that a new alternative therapy—cisplatin-based chemoradiation—is more effective than standard therapy using radiation alone in the treatment of advanced cervical cancer (Rose and Lappas 2000). Using an economic model, Rose and Lappas apply unit costs to resource allocation data derived from the cisplatin-based chemoradiation arms of the five randomized trials and examine the benefits in terms of increased median survival time. Costs per YLS for cisplatin-based chemoradiation regimens varied from US$2,384 to US$28,770 on the basis of published survival and from US$308 to US$3,712 on the basis of estimated survival. Although chemoradiation for advanced cervical cancer would probably be considered cost-effective in most developed countries, analyses that take local treatment settings into account are needed to determine if this result also holds for developing countries.

Palliative Care Interventions. The most basic approach to palliative care for terminally ill cancer patients, especially in low-resource settings, involves using inexpensive oral analgesics, ranging from aspirin to opiates, depending on individual patients' needs. Unfortunately, sufficient supplies of opioid drugs for use in palliative care are often not available in developing countries because of regulatory or pricing obstacles, ignorance, or false beliefs (for more information see http://www.medsch.wisc.edu/painpolicy/index.htm and chapter 52).

Appropriate palliative care for cancer patients may involve a variety of other treatment modalities, including antiemetic drugs to relieve the side effects of chemotherapy, radiation to effect temporary tumor regression, and physical therapy to alleviate disability related to lymphedema following breast cancer surgery. Berthelot and others' (2000) study combines information from several clinical trials and Canadian treatment cost information to perform cost-effectiveness analyses of different ambulatory chemotherapy regimens used for patients with metastatic non-small-cell lung cancer to palliate symptoms and modestly improve survival. They report that vinblastine plus cisplatin resulted in both better survival and lower health care expenditures than best supportive care because it resulted in fewer episodes of rehospitalization.

Van den Hout and others' (2003) study examines the cost-effectiveness of single-fraction versus multiple-fraction radiotherapy for palliative treatment of cancer patients with painful bone metastases. They find that overall medical and social costs for single-fraction radiotherapy for palliative therapy—US$1,144 per patient in medical costs and US$1,753 per patient in total social costs—were lower than comparable costs for multiple-fraction radiotherapy, despite the higher rate of retreatment associated with single-fraction radiotherapy. Whether those results are directly applicable to radiation treatment in developing countries, where single-fraction radiation treatment may be relatively less effective, is unknown. Nonetheless, the results strongly suggest that single-fraction

radiotherapy may be an acceptable, if not preferred, choice of palliative treatment in settings where resources for radiation treatment are relatively scarce and the need for palliative treatment is relatively high.

APPLICABILITY OF COST-EFFECTIVENESS STUDIES FROM DEVELOPED TO DEVELOPING COUNTRIES

Many of the cost-effectiveness studies of cancer control interventions (prevention, screening, and treatment) have been performed in the context of high-income, developed countries; thus, the question arises whether such studies are applicable to health care delivery settings in developing countries. No simple rule is available to indicate how the results of cost-effectiveness studies in developed countries might translate to health care delivery settings in developing countries, but disease incidence and time horizon are major pertinent considerations in relation to cancer prevention and screening interventions. In relation to cancer treatment, other considerations have to be taken into account.

Factors Affecting the Applicability of Cost-Effectiveness Studies of Prevention and Screening

Cost-effectiveness analyses of cancer prevention and screening interventions are complex. Several parameters have a large influence on the results of these studies, including the following:

- age-specific cancer incidence
- all-cause life expectancy and temporal trends of major epidemics
- population age structure
- availability, effectiveness, and costs of cancer treatment
- health system costs of the prevention or screening intervention.

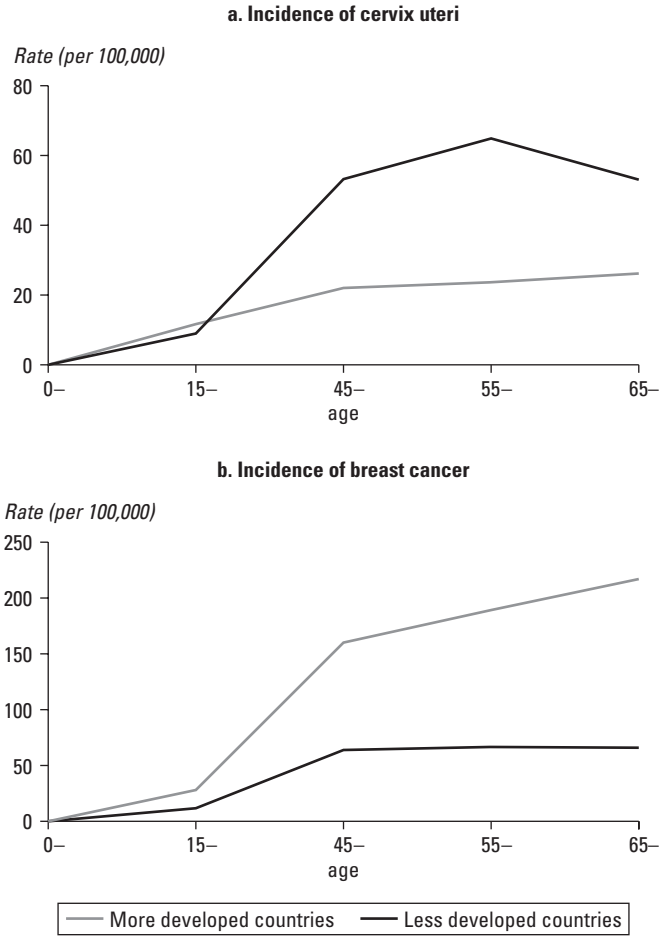
As illustrated by the several examples described in this chapter, those parameters are likely to vary widely between developed and developing countries.

For example, age-specific cancer incidence in the absence of a preventive or screening intervention can have a major influence on the potential cost-effectiveness of a cancer prevention or screening intervention. Generally, the higher the background incidence of the cancer, the more cost-effective the cancer prevention or screening intervention will be. For that reason, the relative cancer incidence patterns in developed and developing countries for the cancer screening interventions described earlier need to be considered.

Figure 29.3 shows age-specific cancer incidence patterns for cervical and breast cancer for developed and developing countries. As the figure shows, the incidence of cervical cancer in developing countries is relatively high in comparison with the incidence of these cancers in developed countries, whereas the incidence of breast cancer is relatively low in developing countries compared with that in developed countries. Given the relatively high incidence of cervical cancer in developing countries, interventions for cervical cancer prevention and screening are likely to be more cost-effective in developing countries rather than developed countries, compared with interventions for breast cancer, all else being equal.

Factors Affecting the Applicability of Cost-Effectiveness Studies of Treatment

Many of the treatments for breast, colorectal, and lung cancer that have been shown to be efficacious in controlled clinical trials have been estimated to have cost-effectiveness ratios in the range of a few thousand U.S. dollars to a few tens of thousands



Source: Ferlay and others 2001.

Figure 29.3 Age-Specific Incidence of Cervical and Breast Cancer, Developed and Developing Countries, 2000

of U.S. dollars per YLS. This range is considered quite favorable in developed countries but might be viewed as less favorable in low- and middle-income countries that face stringent constraints on health care resources. Disease incidence and time horizon do not loom as major considerations in the case of the cost-effectiveness of cancer treatment, because the cost of treatment applies only to those individuals already diagnosed with cancer and considered eligible for a specific treatment, not to a broader population considered to be at risk for developing cancer.

Thus, in low-income, low-cost countries with high mortality rates, because of the lack of primary treatment, the provision of basic cancer treatment may be a cost-effective first step toward cancer control, especially for highly treatable cancers with relatively low incidence in developing countries. For example, using a generalized cost-effectiveness approach, Ginsberg and others (2004) conclude that the provision of basic treatment for colorectal cancer in low-income African countries is likely to be a cost-effective first step toward cancer control.

Nevertheless, issues of economies of scale and scope may be associated with fixed investments in specialized medical equipment and skilled human capital. The centralization and regionalization of cancer treatment may be associated with a higher technical quality of care and might also be associated with the need to use these resources at economically efficient levels. Some cost elements, such as local labor and the availability of generic drugs since initial clinical trials were conducted, will clearly be lower in the contemporary setting of developing countries than in many of the cost-effectiveness studies reviewed earlier.

Finally, developments in cancer treatment, especially in relation to chemotherapy, are extremely dynamic. For example, the 1999 WHO list of essential drugs for cancer therapy (Sikora and others 1999; WHO 2003a), includes 5-fluorouracil as a priority one (essential) drug and irinotecan as a priority three (palliative benefit only) drug for the treatment of colorectal cancer. Just five years later, in many developed countries the following drugs, in addition to irinotecan, have been added to the basic regimen of 5-fluorouracil plus leucovorin for the treatment of colorectal cancer: oxaliplatin, bevacizumab, and cetuximab. Whereas 5-fluorouracil-based treatment of metastatic colorectal cancer increased median survival from 8 to 12 months, the newer drugs increase median survival to 21 months or more, at a significantly increased economic cost. In the United States, the drug cost of 5-fluorouracil-based therapy ranges from US$63 to US$263 for the initial eight weeks of therapy. Adding irinotecan or oxaliplatin increases the drug cost to about US$10,000, and adding bevacizumab or cetuximab adds another US$20,000 to US$30,000 to the cost of initial treatment. If the latter drugs are used over the longer term as envisioned, the average cost of supplying the drugs to a single patient could approach US$300,000. Those estimates do not consider the additional costs of chemotherapy preparation, administration, and supervision and supportive care (Schrag 2004). The situation is similar for other common cancers. Clearly, low- and middle-income countries cannot afford to make the newest cancer drugs widely available to cancer patients; however, this example illustrates the need for periodic updating of available chemotherapy options along with evaluations of the incremental costs and benefits associated with them.

RESEARCH AGENDA

Knowledge about the feasibility, effectiveness, and cost-effectiveness of cancer control interventions by health services in developing countries is extremely limited, partly because of the relative paucity of active research in this area. Work in the area of descriptive epidemiology, especially work based on cancer registry data, dominates the research literature on cancer in developing countries. A second body of literature consists of comparative epidemiology and case-control studies designed to assess the importance of various risk factors for cancer.

Although information from such studies is an essential first step for characterizing the nature and extent of the cancer burden and for monitoring the ultimate effect of cancer control interventions, it does not provide a sufficient knowledge base for designing and implementing cancer control programs. For progress to be made for developing countries, much more work is needed in the following areas:

- *Clinical evaluation studies of cancer control interventions in developing countries.* Clinical evaluation studies of preventive, screening, and treatment interventions that are specifically tailored to the needs and conditions of developing countries would be useful, including controlled clinical trials where possible.
- *Health services research in developing countries.* Health services research designed to characterize the amount, distribution, and organizational structure of health sector resources in developing countries would be helpful, along with research to fill the gaps between current resource endowments and the amount of funding that would be needed to implement the minimally acceptable level of effective cancer control. In developing countries, shortages of the equipment and personnel needed to administer radiotherapy for cancer, for example, have been well documented (Levin, Meghzifene, and Tatsuzaki 2001). However, no systematic analyses are available outside developed countries (Owen, Coia, and Hanks 1997) that project radiotherapy resource needs in terms of clinically effective applications of

radiotherapy, both by cancer site and by the known effectiveness of radiotherapy for primary treatment, adjuvant therapy, and palliative care. Similarly, even though researchers have carried out patterns of care studies that characterize the dissemination of radiation, chemotherapy, and hormonal therapy in many developed countries, comparable information for developing countries is generally unavailable. Health services research studies could also contribute important information about the current structure and organization of primary, secondary, and tertiary care in specific developing countries, with the ultimate aim of modeling and implementing cancer control delivery systems that either are integrated with or supplement existing care delivery systems. Studies of this type are needed to ensure that there is a balance, for example, between resources devoted to screening and those devoted to diagnostic follow-up and treatment. The disappointing performance of cervical cancer screening programs in many developing countries has been due in part to the lack of effective diagnostic follow-up and treatment following screening.

- *Country-specific economic evaluation studies.* Country-specific studies need to be done that assess resource requirements, economic costs, effectiveness, and ultimately cost-effectiveness of cancer control interventions adapted or tailored to the needs and requirements of low- and middle-income settings. Heuristic extrapolation is a first analytical step in this direction, but such studies can indicate only whether more direct and realistic studies are needed.
- *Studies of innovative health care information and communications technology.* More research is needed to determine if technological advances, such as computerized image reading or long-distance consultation by oncology specialists, facilitated by telemedicine communications technology, might alter the cost-effectiveness equation by raising quality, by lowering costs, or both. For remote localities or small, low-income developing countries, training and employing local expertise or advanced equipment for every aspect of cancer control may not be necessary if advanced communication and information technology could be used to facilitate virtual collaboration.

CONCLUSIONS

Our ability to draw any conclusions about the cost-effectiveness of cancer control interventions for low- and middle-income developing countries is limited, because most cost-effectiveness studies in this area have been conducted in high-income, developed countries. Cancer control interventions that appear to be cost-effective in high-income countries may not be cost-effective in low-income countries, even when the lower cost of providing health services is taken into account.

A useful way to draw inferences about the relative cross-country affordability of interventions is to translate cost-effectiveness ratios into percentage of per capita gross national product (GNP) per YLS (WHO 2001a). Our preliminary analysis of breast cancer screening in India, for example, suggesting an absolute cost-effectiveness level for screening mammography of about US$2,000 per YLS, compared with about US$3,000 per YLS in the Netherlands. At about 10 percent per capita GNP per YLS, screening mammography might be considered to be extremely cost-effective for the Netherlands. In India, however, we found a CE estimate equal to 400 percent per capita GNP per YLS suggesting that national policy makers would be much less likely to consider screening mammography as a viable intervention given India's health care budget constraints. However, they might well consider a CBE breast cancer screening program, at about 200 percent per capita GNP per YLS in India, to be moderately affordable if the program were definitively established to be effective.

For middle-income developing countries that have cancer incidence rates similar to those in high-income developed countries, the results of cost-effectiveness analyses from the developed countries may be more relevant, although further analysis clearly is needed. The case study of cervical cancer control that was cited earlier suggests that for low-income countries tailored cancer control interventions may need to be developed that would be both cost-effective and affordable. However, that suggestion does not imply that low-tech approaches should be uncritically embraced and assumed to be cost-effective. Until recently, education campaigns to promote breast self-examination were widely advocated as the low-tech alternative to screening mammography for breast cancer control in low-income countries; however, the best current evidence now indicates that such campaigns have no effect on breast cancer mortality (Semiglazov and others 1999; Thomas and others 2002).

In cancer treatment interventions, the cost-effectiveness of initial surgical treatment for treatable cancers, such as breast, cervical, and colorectal cancer, may be in the relatively favorable range of a few to several thousand dollars per YLS, which indicates that such interventions are likely to be cost-effective for middle-income countries and are possibly cost-effective for low-income countries. Although cost-effectiveness ratios for some of the approaches to adjuvant therapy that use conventional radiation and drugs also fall within this relatively favorable range, others are in the range of tens of thousands of dollars for each YLS. Thus, these forms of treatment would likely be considered potentially cost-effective and affordable in middle-income countries but not in low-income countries; however, more detailed examinations of specific cost conditions and available resource endowments for the delivery of cancer treatment services are needed to confirm these preliminary impressions. As with the case of cervical cancer control,

treatment interventions that are tailored to the conditions of low-income countries might be shown to be efficacious and more economically attractive than treatment approaches that are transported directly from developed countries; however, research in this area is lacking.

Time Horizon and a Balanced Approach to Cancer Control Programs

The time horizon for cancer prevention and screening interventions is highly relevant to policy makers and health system planners, yet reports on the cost-effectiveness of such interventions often omit information about time horizons. For example, interventions that involve cancer control agents that prevent cancer cases that would have otherwise occurred many years after the preventive action, such as HPV vaccination, have a long time horizon. Similarly, the favorable cost-effectiveness of preventive screening for stomach cancer is not apparent until four decades following the initiation of the intervention. In the case of the 25-year program of CBE in India analyzed earlier, only about 10 percent of the benefits in terms of breast cancer deaths prevented would have been realized after 10 years of program operation. Decision makers must understand and take these time horizons into account when interpreting and acting on cost-effectiveness ratios; however, the long time horizon for cancer prevention and screening interventions is, in itself, not an argument against the application of such interventions. In some cases, countries that are more recent entrants into the field of cancer control may be able to benefit from the experience of developed countries and from the dynamic technical progress in this area to go directly to new innovations. For example, they might be able to implement HPV testing right away as the basis for cervical cancer screening, bypassing cervical cytology. Achieving the optimal temporal balance in comprehensive cancer control represents a daunting challenge to planning, evaluation, and implementation.

Start Small, Scale Up Smart

Because the current understanding of the effectiveness, optimal resource mix, and cost of many cancer control interventions is incomplete and uncertain, especially in relation to low- and middle-income countries, developing countries should start small. By starting small, they can gain knowledge from pilot programs that are well documented with regard to organizational and process factors; that are conducted in controlled settings, if possible; and that are monitored for efficiency, performance, and effectiveness. Thus, for example, new screening or treatment programs can be initiated in focused geographical areas or specific facilities with known and well-characterized target populations, and their performance and outcomes can be compared with matched control areas or facilities. Developing countries should consider scaling up their regional or national programs only after the pilot programs have been shown to perform well.

Starting small also might entail applying an initial pilot program to a limited age range that is estimated to yield the most benefits per resource use or to a limited group of high-risk individuals defined by various risk characteristics, such as first-degree relatives of people with cancer. Indeed, various versions of this approach have characterized the dissemination of many cancer control interventions in developed countries. Organized breast cancer screening programs in some European countries, for example, were first implemented as pilot programs in specific regions and evaluated against control communities (Fracheboud and others 2001; Olsson and others 2000; van der Maas 2001), and regional and national programs were initially limited to the age groups, screening procedures, and screening frequencies estimated to be the most cost-effective. The programs were later extended, in terms of more intensive procedures, more frequent screening intervals, and wider age groups, after monitoring and analysis of initial program performance indicated that the incremental cost-effectiveness of these extensions would be favorable (Boer and others 1995; Shapiro and others 1998). The United Kingdom has taken a similar approach to colorectal cancer screening (Steele and others 2001).

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